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The Surgical Treatment of Mitral Stenosis (Mitral Commissurotomy)*

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Stenosis of the mitral valve has long challenged the therapeutic ingenuity of the medical profession. It has seemed unreasonable that young persons in otherwise satisfactory health should be condemned to a life of invalidism and early death. Success in treating strictures and stenoses in other organs has suggested that such a simple mechanical defect should not present an insuperable problem.

However, fear of surgical attack upon the heart, discouraging results of early attempts, and a general lack of appreciation among the medical profession of the extreme seriousness of this disease, have greatly hampered those interested in the problem. Many internists, among whom are cardiologists, feel that with proper medical management and limited activity these patients may live a normal span of life. It is true that most older practitioners know of a case or two of mitral stenosis which has survived to an advanced age. Unfortunately, these men do not have any roughly accurate idea of the much larger number of cases which have died at an early age. It is also notable that these same older patients will admit that they have not especially enjoyed their prolonged life of limited activity. The author has recently been consulted by a woman of 58 and another of 62 who have been "successfully" treated medically for 25 and 28 years, respectively. They now, at their advanced age, being no more limited than they were 10 years ago, are futilely petitioning for a chance at surgical relief.

The serious prognosis of mitral stenosis can hardly be properly

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presented statistically, since cases vary in severity, and since death is often wrongly attributed to some other heart condition, to asthma, or to pulmonary tuberculosis with hemorrhage. This latter syndrome (mitral stenosis with serious hemoptysis) has been shown by Wolfe and Levine in 1941¹ to have a mortality of 66 per cent within 3 years. This has been brought home dramatically to the author, who recommended surgery in two such cases eight and six weeks ago, respectively. Both at first accepted surgery and then changed their minds because of the presumed risk. Both have already died of pulmonary hemorrhage.

With such a dismal outlook, it is time to take steps to differentiate those cases which are mild or non-progressive from those who will not have any useful existence. It then is incumbent upon the profession to learn how to alleviate the severe cases.

Levine² has stated that the average period of time between the onset of the signs of congestive failure and death is four and three-fifths years. And this in the vast majority of cases appears in young individuals, between 15 and 30 years of age.

It is my belief that there are at least one million cases of mitral stenosis in the United States, one-quarter of which are suitable for surgery. This brings the problem of management within the domain of not only the cardiologists and internists, but also of every general practitioner.

The cause of disability and death in mitral stenosis is related to (1) right ventricular failure (congestive); (2) pulmonary vascular congestion leading to fibrosis, pulmonary edema, and hemoptysis varying from slight to fatal; (3) inability of the left ventricle to furnish sufficient blood to the body. The pulmonary vascular congestion is due to damming back of blood behind the stenotic valve, producing great distention of the left auricle and hypertension of the entire pulmonary vascular bed, especially on the venous side. These pulmonary symptoms are often most prominent and have led certain investigators to deviate from the direct line of approach to the pathology. Thus, the observations of Lutembacher³ that cases of mitral stenosis associated with a congenital interauricular septal defect are clinically milder than those without such defects, have led to various attempts to produce such a defect. The production of such septal defects and of anastomoses between the azygos vein and a pulmonary vein (which accomplishes the same type of shunt) have been successfully accomplished experimentally both in our animal laboratory and others. It has remained for Dr. Richard Sweet⁴ of Boston to actually perform such an anastomosis successfully in clinical human cases. The shunt permits the high pressure in the pulmonary veins and left auricle to be reduced toward an equilibrium with

the systemic venous pressure. Thus the pulmonary hypertension is markedly reduced with alleviation of all pulmonary congestive symptoms (hemoptysis, pulmonary edema). The patients with this pulmonary syndrome become more comfortable. Both Harken⁵ and the author have opened the interauricular septum in human cases.

However, it must be remembered that the left auricular hypertension is really the main compensatory mechanism which helps force blood through the narrowed mitral orifice. The removal of this hypertension, while it may relieve the most prominent symptoms, actually leads to a reduction in the amount of blood which passes through the valve into the left ventricle. Thus the reduced ventricular output is still further reduced and systemic congestion is somewhat increased by the shunt.

It appears that some procedure which would permit a greater amount of blood to enter the left ventricle must be the logical method of attack. This might be a plastic procedure upon the mitral valve (including dilatation, valvulotomy, or partial valvulectomy), or the insertion of a mechanical valve (plastic or metal) into the mitral ring, or some method of bypassing the valve entirely. This latter (bypassing) has been successfully accomplished in the laboratory by Litwak⁶ who successfully communicated the left inferior pulmonary vein to the left ventricle by a free vein graft.

Of these methods, some type of plastic procedure upon the valve has seemed most promising. An open method of attack is at present hampered by the lack of a suitable mechanical pump to carry on the circulation during the operative procedure. However, Templeton, Gibbon, and Allbritten⁷ have had some success by the open technic in animals. Furthermore, any involved or extensive plastic repair would probably break down by virtue of the necessarily constant cardiac function during the healing period. Thus a closed type of operation which permits continuance of normal circulation and accomplishes only a rather simple plastic procedure would seem to be most desirable at present.

A review of the reports in the literature by Cutler and Beck⁹ in 1929 of operations upon the aortic and mitral valves revealed that of the first 10 cases of mitral stenosis subjected to operation, one died during insertion of an instrument into the left auricular appendage, two were subjected to finger dilatation of the mitral valve after insertion through the left auricular appendage (both cases lived and were improved), three cases were treated by tenotome division of a valve cusp (one lived 4½ years and was much improved), and five cases were subjected to partial valvulectomy by the cardiovalvulotome (all died).

It was interesting to note that of the two cases of manual dila-

tation of the valve reported, both survived the procedure and were improved. Of three cases of simple valvulotomy (cutting across a valve cusp), only one case survived. Of five cases of partial valvulectomy (by valvulotome), none survived. Since simple manual dilatation actually meant the partial tearing open of the fused portions of the valve commissures, it closely resembled the operative procedure which we are now presenting. Cutting across a valve cusp, on the other hand, would either produce little enlargement of the valve opening if of slight extent, or marked regurgitation if of great extent. Therefore, it would be either useless in alleviating the stenosis or extremely dangerous because of the production of sudden severe regurgitation. Partial valvulectomy as practiced with the cardiovalvulotome was a blind, crude procedure, frequently leading to severe unexpected damage to other parts of the heart, and even if successful in application, led to severe mitral regurgitation.

Allen and Graham⁹ attempted to improve the control of valvulotomy by devising a cardioscope in 1923.

After 1929 no more surgical attempts were made until 1945. Both Dr. Dwight Harken⁵ and Dr. Horace Smithy,¹⁰ as well as the author, have made recent operative attempts to improve cases of mitral stenosis. Our clinical experience with the surgery of the mitral valve has been with five cases to date.

During the past eight years the author and his associates have performed diverse and repeated operations upon the mitral valve of some 60 mongrel dogs. Several conclusions have been reached: (1) The approach through the left auricular appendage is the most satisfactory one since there is less danger of arrhythmia, greater ease of entering the valve, and greater ease in controlling hemorrhage. Entrance through the apex of the left ventricle leads to more arrhythmia, greater difficulty in entering the mitral valve orifice because of impinging upon the chordae tendinae, and greater difficulty with hemorrhage. (2) Production of an appreciable degree of sudden mitral regurgitation is tolerated poorly by dogs. Thus extensive cutting of the anterior cusp of the mitral valve is nearly always attended by operative mortality. It would seem that regardless of the reported observation that clinical mitral regurgitation is less crippling than clinical mitral stenosis, these sick human hearts will not tolerate the sudden production of a large mitral regurgitation very well. (3) The accurate placement of an instrument to divide a mitral valve depends upon actually palpating the valve and instrument from within the auricle at the time of operation. Thus, whether the cutting instrument is inserted through the ventricle or auricle, it is necessary that the right index finger be passed through an incision

in the left auricular appendage to palpate the valve and cutting edge. (4) The palpating finger is well tolerated in the left auricle and even within the actual valve orifice unless obstruction of the passageway is produced. Thus, there is no particular danger in palpating the valve, and therefore blind surgery to the valve is no longer necessary. (5) Dogs do not seem to develop mitral stenosis and the actual human type of pathology cannot be well reproduced in animals. There is, therefore, a limit to the analogies between experimental and clinical studies. (6) A considerable variety of instruments may be employed for commissurotomy. We now prefer a backward cutting punch (Figure 1) and a scalpel with a hooked blade (Figure 2). With the experience gathered from animal work it remains only to reconsider the pathology of mitral stenosis to arrive at the most effective method of direct attack upon the stenotic valve.

The pathology of clinical mitral stenosis varies. In most cases it is due to rheumatic fever. The valve cusps become thickened, shortened, and fibrotic. The cusps appear to fuse at the commissures so that the opening becomes a shortened and narrowed slit in a thickened, fibrotic plaque. Through this rigid slit a certain amount of regurgitation occurs. At times there is calcification of the valve edges. If the calcification is extensive it renders this plaque hard. The calcification is often increased at one point, perhaps due to calcification of a former vegetation or verrucca. Such a localized involvement may by itself obstruct two-thirds of the normal valve opening, and thus be responsible



FIGURE 1: Backward cutting punch with trocar and cannula.



FIGURE 2 a

FIGURE 2 b

FIGURE 2 c

Figure 2 a: Right and left curved commissurotomy knives and cannula.—Figure 2 b: Commissurotomy cannula on right index finger.
Figure 2 c: Commissurotomy knife in cutting position.

for the stenosis of an otherwise not too distorted valve. An interesting and important observation at autopsy study of these valves is that the *plaque of thickened fibrotic tissue is surrounded by a margin of fairly normal valve tissue* (Figure 3). It occurred to the author that it might be possible to cut such a plaque completely in two by two incisions at the commissures of the valve

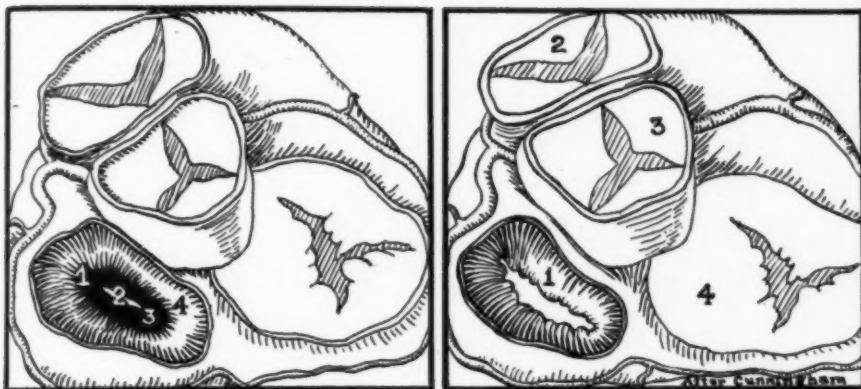


FIGURE 3 a

FIGURE 3 b

Figure 3 a: *Stenotic Valve*: 1) Lateral commissure, 2) Mitral orifice, 3) Fibrotic zone, 4) Normal tissue.—Figure 3b: *Normal Valve*: 1) Mitral valve, 2) Pulmonary valve, 3) Aortic valve, 4) Tricuspid valve.

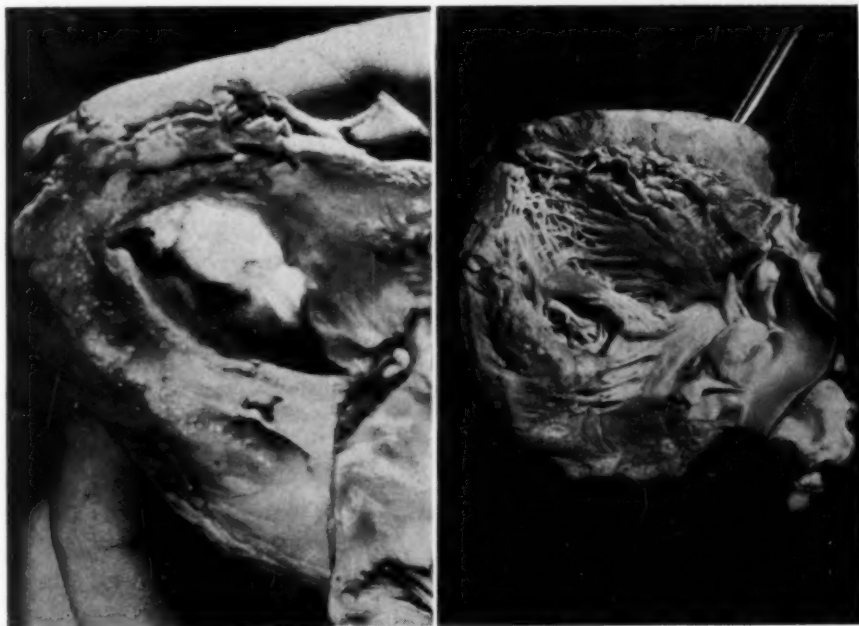


FIGURE 4

FIGURE 5

Figure 4: *Stenotic valve opened by lateral commissurotomy*.—Figure 5: *Superior ventricular aspect of aortic cusp of mitral valve after commissurotomy showing maintenance valvular support by the chordae-tendinae*.

STATISTICAL TABLE OF OPERATIONS FOR CHRONIC VALVULAR DISEASE UP TO 1929

| Case | Author or Operator | Date | Diagnosis | Method or Instrument | Results |
|------|---|----------|--|----------------------|--|
| 1 | Doyen | 1913 | Congenital pulmonary stenosis; patent inter-ventricular septum | Tenotome | Died, few hours after operation |
| 2 | Tuffier | 1914 | Aortic stenosis | Finger dilatation | Recovery, improved |
| 3 | Cutler and Levine: Boston M. & S. J. 188:1023, 1923 | 5/20/23 | Mitral stenosis | Tenotome | Died, 4 years and 6 months after operation |
| 4 | Allen and Graham | 8/7/23 | Mitral stenosis | Cardioscope | Operative death |
| 5 | Cutler, Levine & Beck | 10/7/23 | Mitral stenosis | Tenotome | Died, 10 hours after operation |
| 6 | Cutler, Levine & Beck | 1/12/24 | Mitral stenosis | Tenotome | Died, 20 hours after operation |
| 7 | Cutler, Levine & Beck | 2/25/24 | Mitral stenosis | Cardiovalvulotome | Died, 6 days after operation |
| 8 | Cutler, Levine & Beck | 6/11/24 | Mitral stenosis | Cardiovalvulotome | Died, 3 days after operation |
| 9 | Souttar | 5/6/25 | Mitral stenosis and aortic insufficiency | Finger dilatation | Recovery, living and improved |
| 10 | Pribram | 11/14/25 | Mitral stenosis and aortic vegetative endocarditis | Cardiovalvulotome | Died, 6 days after operation |
| 11 | Cutler & Beck (first report) | 12/8/26 | Mitral stenosis | Cardiovalvulotome | Died, 15 hours after operation |
| 12 | Cutler & Beck (first report) | 4/15/28 | Mitral stenosis | Cardiovalvulotome | Died, 3 hours after operation |

TOTALS: 12 cases

1 aortic stenosis, acquired
1 pulmonary stenosis, congenital
10 mitral stenosis, acquired

2 finger dilatations
4 tenotome attempts
5 cardiovalvulotome attempts
1 cardioscope attempt
Mortality, 83 per cent

opening (Figure 4). These incisions should be extended well into the normal valve tissue margin so that the two halves of the plaque could separate freely, being hinged by soft valvular tissue at either extremity. In the pathologic specimens such incisions appeared to accomplish this result. It was also apparent, since the chordae tendinae were left intact (Figure 5), that increase in fluid pressure on the ventricular side would force the rigid halves of the valve together, while increase in fluid pressure on the auricular side would cause them to separate. It seemed that such incisions could relieve a mitral stenosis without increasing the amount of regurgitation which already existed because of the rigid valve opening.

CASE REPORTS

Case 1: Our first clinical case was W.S., a man of 37 years who had been severely incapacitated for 16 years and who had had several severe episodes of hemoptysis. On November 14, 1945 his left anterior chest was opened through the third left anterior interspace at Hahnemann Hospital, Philadelphia, Pennsylvania. The pericardium was opened and the distended left auricular appendage practically herniated out of the pericardial sac. A purse-string suture was placed around the tip of the auricular appendage preparatory to inserting a trocar and canulla for passage of the backward cutting punch. As the trocar and canulla were inserted the purse-string suture was pulled upon and tore out of the friable and distended auricular appendage. Severe bleeding occurred and a large clamp was hastily applied to the appendage close to its origin. The clamp was completely closed—and cut through the appendage wall. Attempts to reapply a clamp proximally were temporarily successful, but it was impossible to get mattress sutures to hold in the friable auricular tissue under tension enough to approximate the edges of the auricular defect. The patient died on the operating table of hemorrhage, no valvulotomy having been performed. We have ever since realized that the human auricular appendage in mitral stenosis is friable and entirely unlike that of a normal dog. We no longer permit a hemostat to be closed on an auricular appendage beyond the first tooth of the ratchet, and prefer not to actually close the ratchet.

Case 2: Our next case was W.S., a 29 year old married female who had been a cardiac invalid for 11 years, and who had been in congestive failure on several previous occasions during the preceeding 7 years. On this occasion she failed to respond to the usual medical measures and remained in a precarious state with engorged liver and ascites in spite of digitalis and mercurial diuretics. Since she was deemed hopeless, her physicians felt that she might be subjected to valvulotomy. At operation on June 12, 1946 the heart was approached through a left anterior thoracic incision, and the pericardium was incised. Up to this point the blood pressure was approximately 60/50 mm. mercury, and the surgeon began to seek an honorable way of abandoning the procedure. However, the medical consultants stressed that she would undoubtedly die from the anaesthesia and exploration unless some relief of the stenosis could be obtained. Therefore, the left auricular appendage was entered by

trocár and canulla, and the backward cutting punch was inserted through the canulla. It was well tolerated by the heart, but could not be inserted through the mitral valve orifice. Several firm irregularities were encountered by the instrument but no mitral opening could be found. Therefore, the trocár and canulla were removed, the opening in the auricular appendage was enlarged, and the right index finger was inserted. The mitral valve was found to be a tiny slit which would not admit the tip of the index finger. There was considerable calcification about the valve mouth. This had been palpated by the instrument, but the actual orifice was too small to admit the punch (about the size of a small lead pencil). The valve was forcibly dilated digitally, so that the finger could be inserted into the orifice to the second phalangeal joint. Care was taken not to obstruct the opening for longer than three heart beats at a time. The valve appeared to tear open at both commissures. The thrill which was prominent prior to dilating the valve, immediately disappeared. The blood pressure promptly rose to 80 systolic and the patient's condition began to improve. Because of the improvement and the desperate nature of the risk, the finger was withdrawn and the auricular appendage ligated without any attempt at incising the valve.

The patient's condition continued to improve so that the blood pressure was 130 systolic at the conclusion of the procedure. The diastolic murmur of mitral stenosis was entirely gone subsequent to surgery, but a systolic murmur appeared. Some felt that this might be due to mitral regurgitation, but the author is doubtful. Improvement was continued for 30 hours. After that the condition began to deteriorate and she died rather quickly 48 hours after surgery. Autopsy revealed a greatly dilated heart, 300 cc. of serous fluid in the pericardium, and some plastic pericarditis (sterile). The mitral valve showed evidence of having been torn open at both commissures, but the tears had not extended into the normal marginal valve tissue. The torn surfaces had therefore not separated much, and had become agglutinated by fibrin which accumulated in the orifice and gradually reduced the effective mitral opening to probably a smaller size than that existing at the time of operation. It was difficult to imagine any degree of regurgitation through that valve orifice. No anticoagulant therapy had been employed. As a result of the autopsy findings, the idea was conceived of performing what had been later termed "commissurotomy" by Dr. Thomas Durant of Philadelphia.

Case 3: The next patient was W.W., a white male 38 years of age, who had been having episodes of severe hemoptysis over a period of 1½ years. In fact, he had had a segmental resection of the right lung performed for bronchiectasis one year previously, in the belief that his hemorrhages were of pulmonary origin. However, after 8 months his hemorrhages had returned in an exsanguinating form. Re-study then revealed that a marked enlargement of the heart had taken place during the interim and typical evidences of severe mitral stenosis were now evident. The patient was also showing early signs of decompensation. On March 22, 1948 at the Memorial Hospital in Wilmington, Delaware, the left 4th anterior rib was removed and the pericardium was opened. Pressure in the left auricular appendage was 240 mm. H₂O. The auricular appendage was incised and the right index finger was inserted. The mitral valve was found to be obstructed mainly by a hard calcific nodule roughly 15 mm. square which occupied the medial 2/3 to 3/4 of the mitral orifice. A marked presystolic thrill was present. The rest of the valve orifice was

non-calcified and leathery. It was too tight to permit insertion of the finger tip. A non-detachable knife with a curved handle was inserted along the dorsum of the palpating finger within a second glove until it perforated the end of this outer glove (Fig. 3). It was then guided by the finger to cut the lateral commissure of the mitral valve orifice. The shape of the knife blade permitted it to repeatedly disengage from the valve, but it was possible to markedly loosen the valve opening. The author was somewhat dissatisfied by the amount of opening, but the calcified nodule prevented any incision on the medial commissure. Since the finger could now readily enter the ventricle, and since the thrill had completely disappeared, the finger was withdrawn and the auricular appendage was carefully oversewn. The patient's condition remained excellent throughout the operation. There was no arrhythmias, and the only weakening of the radial pulse was during actual obstruction of the valve by the finger. Continuous electrocardiograms during the operation showed only minimal abnormalities. Procaine (1/10 of 1 per cent) was administered by drip during the operation.

Because of the bitter experience with the previous patient, it was decided to use anticoagulant therapy. Therefore, the clotting time was kept at between 20 and 30 minutes by a continuous drip of heparin in saline. The patient did reasonably well until the second postoperative day, when evidence of hemorrhage into the left pleura required repeated thoracenteses. Heparin therapy was discontinued. When the red blood count had dropped to 2,450,000 on the third postoperative day, it was felt necessary to transfuse him, and this was done, 2600 cc. blood being given. Unfortunately, there was a misunderstanding regarding orders pertaining to fluid balance, and a total of 7,400 cc. of fluid by mouth and parenterally on the fourth postoperative day, and 1,500 cc. on the fifth postoperative day was administered. As a result the patient became markedly edematous. At about 4 p. m. he suddenly developed pulmonary edema and expired. Autopsy revealed over 1,000 cc. of blood in the left pleura, a dilated heart, and extensive pulmonary edema. The hemorrhage had apparently occurred from the chest wall in spite of extreme care in hemostasis during the chest wall closure. The auricular appendage had not bled, and was completely occluded by a well attached thrombus (a constant finding in dogs subjected to this operation). The incision in the lateral margin of the mitral valve was approximately $\frac{1}{4}$ inch in length and did not extend completely through the fibrotic plaque. There was no fibrinous sealing off of the valve orifice.

In reviewing this case, we considered that the following errors had been made: (1) Perhaps the use of the heparin therapy was unwise, since it had required the administration of a considerable volume of fluid, and since it undoubtedly played a major role in the secondary intrapleural bleeding. (2) The use of saline rather than glucose solution as a vehicle for the heparin. (3) Inadequate incision in the lateral commissure of the valve, partly due to the repeated disengaging of the knife blade on account of its shape. The medial commissure could not be cut because of the large calcification. (4) Unwise and excessive fluid therapy. (5) Perhaps accepting a case for surgery who had had diminished contralateral lung function from previous disease and partial lung resection. It was the consensus, however, of all physicians concerned that if we had just returned the patient to bed postoperatively, and not treated him, recovery would have followed.

Case 4: The next case was J.R., a 32 year old white male who had had advanced mitral stenosis for 7 years. During the past 1½ years he had been in chronic congestive failure, although ambulant much of the time. Digitalis and mercurial diuretics did not completely control the congestion. Since his prognosis was extremely grave without surgery, it was finally decided to attempt a commissurotomy. On June 10, 1948 at the Philadelphia General Hospital he was anesthetized with endotracheal ether and oxygen. He was placed in the face-down position and the left posterolateral incision was made. It was difficult for the anesthetist to maintain adequate oxygenation because of extremely limited vital capacity. The 5th rib was removed and the thorax entered through its bed. The lung was totally and extensively adherent to the chest wall, diaphragm, and pericardium. These adhesions were carefully dissected free and the lung was retracted upward. The pericardium was incised anterior to the phrenic nerve. Procaine (1/10 of 1 per cent) was administered by intravenous drip (20-80 drops per minute) 2 per cent procaine was flushed in the pericardium. However, the least touching of the heart, either ventricle or auricle, was followed by frequent extrasystoles and other irregularities. Because of this extreme irritability of the myocardium, no attempt at valvulotomy was made. The surgeon became worried and suggested abandoning the procedure at that time. The staff felt that this would be the last opportunity for surgery to be utilized in this man. Intravenous atropine did not relieve the myocardial irritability, nor did 50 mgm. doses of procaine intravenously. Intravenous quinidine was administered slowly by personnel experienced in its use. Before completion of the injection the heart rate had become slow, so the quinidine was discontinued. The systoles became weaker and stopped.

Immediate manual massage restored regular contractions which ceased after a few minutes. Massage was repeated. After that, various stimulants, venesection, artificial respiration, etc., were used. After the heart had been revived by massage a number of times and had failed as many, it was suggested that he might improve if the left ventricular output was increased by opening the mitral valve. Since all was already lost, the auricular appendage was opened and the left index finger was inserted into a tight mitral orifice containing calcium deposits. It was widely dilated, and the finger withdrawn. No instruments were used. The auricular appendage was ligated. After massage had again reestablished a temporary heart beat, it was evident that the left ventricle had become considerably enlarged. However, in spite of repeated massage and all recognized forms of drug stimulation, no permanent restoration of cardiac function could be accomplished. At no time did ventricular fibrillation supervene.

Autopsy was obtained and revealed considerable fibrosis of the myocardium but no evidence of Aschoff bodies nor active rheumatic myocarditis. Since activity of the rheumatic process was not responsible for the extreme myocardial irritability we must look elsewhere for an explanation. In view of the pleural adhesions and the thickened fibrotic lung tissue, and in consideration of the anesthesia difficulties, it is the author's opinion that hypoxia of the body generally and the heart specifically was probably responsible.

We do not consider this a death attributable to mitral valve surgery, since death and an irreversible state had apparently become established well before a last ditch emergency dilatation of the valve was performed.

Undoubtedly this man was too bad a risk for mitral surgery. The pre-operative ballistocardiogram had revealed a poor cardiac output, increased only slightly on exercise.

Case 5: C.W., a 24 year old white housewife, had been known to have a heart murmur for 17 years and mitral stenosis for 24 months. She had had gradual and progressive onset of dyspnea on exertion and had an attack of congestive failure in November 1947. Since that time she had been on extremely limited activity and received a daily maintenance dose of digitalis. On May 17, 1948 she was admitted to Episcopal Hospital in Philadelphia for study preliminary to a possible mitral commissurotomy. She had a typical loud presystolic mitral murmur and thrill. Interestingly enough, all of her clinical and laboratory studies, including ballistocardiography *at rest*, revealed fairly normal conditions. However, she did show marked enlargement of the left auricle (Fig. 5), and was limited in exercise tolerance. The full extent of this limitation was not appreciated until the ballistocardiographic studies were repeated after exercise. Dr. Gordon Ring of the Physiology Department of Temple University was then able to show that her maximum cardiac output on exercise was only double that of her resting needs. Normally cardiac output on exercise will increase many fold. It is our belief that ballistocardiographic studies at rest and on exercise are the only truly dependable objective means of evaluating the functional status of the heart in mitral stenosis. Venous pressure was 111 mm. H₂O. Circulation time 12 minutes arm to lung and 20 minutes arm to tongue. Operation was performed on June 10, 1948. The left anterolateral approach was chosen and the 3rd rib was resected. The pericardium was opened anterior to the phrenic nerve. Pressure in the left auricle was 280 mm. H₂O. Procaine 2 per cent was applied in the pericardium. Procaine (1/10 of 1 per cent) was given by continuous intravenous drip. The auricular appendage was opened and the right index finger, covered by two gloves, was introduced. Between the gloves was a special hooked knife with malleable handle (devised since our experience with case 3). The mitral valve was found to be small, just admitting the tip of the finger. It was not calcified and had a leathery feel, more like kid-skin than cow-hide. It was displaced high up anteriorly. The hooked knife was inserted through the valve orifice and engaged on the lateral commissure under direct digital guidance. The knife was then drawn backward an inch, widely dividing the commissure. The finger was now inserted through the cut valve and some fine remaining fibrous strands were broken up. The valve was now widely patent. The finger was withdrawn and the auricular appendage ligated. The chest wall was closed with drainage. The entire operation had taken 80 minutes. During the period of cutting and dilating the valve, the blood pressure fell and the heart function became slow and labored. No arrhythmia developed. Enlargement of the left ventricle was immediately evident. No anticoagulant or postoperative intravenous therapy was permitted.

Postoperatively the previously marked presystolic murmur was absent. A pericardial friction rub was present on the first and second days postoperative but was gone by the third. She was out of bed on the third day, and walking the fourth. Her greatest difficulty was inability to void for four days postoperatively. On the seventh postoperative day the patient had no cardiac murmur audible to the author. The pulmonic second

sound remained accentuated. She was asymptomatic and felt she was better than she had been for years.

Because of her evident good condition she was transported without incident by train to a 1,000 mile distant medical convention for presentation in person.

No murmur is now present. P_2 is still loud. She is ambulant and comfortable. Unfortunately, it is too early (8 days postoperative) to repeat the ballistocardiography on severe exercise.

(February 1, 1949: Patient is continuing to do well 7½ months subsequent to surgery. She is now able to perform all her own housework. Her ballistocardiographic studies reveal marked improvement in cardiac output on exercise. The P_2 is much less prominent. She has taken no digitalis for 5 months.)

SUMMARY AND CONCLUSIONS

1) Surgical technique and methods and anesthesia have now advanced to the point where intracardiac manipulations may be undertaken with reasonable safety.

2) The mitral valve is best approached through the left auricular appendage by an anterolateral approach. Approach through the apex of the left ventricle is less desirable, in our opinion.

3) Accurate surgical maneuvers depend upon control by vision or digital palpation. In closed surgery of the mitral valve digital palpation through an opening in the left auricular appendage is the logical method of control.

4) Commissurotomy enlarges a stenotic mitral valve orifice and permits valvular function without an appreciable increase in the pre-existing amount of mitral regurgitation.

5) Three cases of mitral valve surgery are presented with one survivor who shows a gratifying early postoperative result. One other case could undoubtedly have been salvaged with our present knowledge, and one case probably was too advanced to help. Two cases of mitral stenosis in which surgery was planned and started but not completed are described.

6) We believe that the operation of commissurotomy has great value in certain cases of mitral stenosis. The selection of cases should undoubtedly be limited to those with essentially single valve lesions in which all rheumatic activity is healed. It is doubtful in the present state of our knowledge whether cases in chronic or acute congestive failure should be operated. Certainly results will be poorer in this group. One of the most urgent indications for surgery is hemoptysis, especially if severe.

7) We believe that commissurotomy is preferable to a shunt operation (azygos-pulmonary vein anastomosis, or opening of the interauricular septum), because the latter merely relieves pulmonary symptoms by destroying one of the natural compensating mechanisms. What is the gain if the signs and symptoms of pul-

monary congestion are relieved and yet the patient goes on to systemic circulatory failure? Or if the left ventricular output is so reduced by loss of its compensating mechanism that the patient's physical activities are still more limited? However, in a hypothetical case where the opening of the valve might not sufficiently reduce pulmonary congestion (due perhaps to too limited incision of the valve commissures) we would not hesitate to perform such a shunt if the pulmonary symptoms endangered life. It is our belief that a high pressure in the left auricle is helpful postoperatively in maintaining separation of the valve cusps after commissurotomy. If a shunt is performed before the valvular surgery, there is undoubtedly a much greater tendency for the raw edges of the commissure to seal together and re-establish the mitral stenosis.

8) We feel that preoperative digitalization, quinidinization, and the use of intravenous procaine during surgery are valuable in supporting cardiac function and in preventing arrhythmia. Antibiotics are given to prevent infection of the wound and of the cut valve surfaces (subacute bacterial infection). Apparently anticoagulant therapy is dangerous and unnecessary.

9) We believe that ballistocardiography before and after exercise offers us the best single objective measure of ventricular output and reserve.

February 1, 1949: Since this time, 5 additional patients have been subjected to this operation. Two are doing very well. One died 2½ months after surgery. One died of an error in technique at operation (cutting across a valve leaflet). One did very well for 6 days but died suddenly of a cerebral arterial embolus. Clotting had occurred in the sutured left auricular appendage. We now ligate the appendage at the base to prevent this.

RESUMEN Y CONCLUSIONES

1) Las técnicas y los métodos quirúrgicos y la anestesia han avanzado hasta tal punto que es posible llevar a cabo manipulaciones intracardiacas con razonable seguridad.

2) La mejor vía de entrada a la válvula mitral es a través del apéndice auricular izquierdo en una dirección anterolateral. En nuestra opinión es menos deseable entrar a través del vértice del ventrículo izquierdo.

3) Las maniobras quirúrgicas exactas dependen del directo control visual o del palpamiento digital. En la cirugía cerrada de la válvula mitral, el método lógico de control es el palpamiento digital a través de una abertura en el apéndice auricular izquierdo.

4) La comisurotomía ensancha el orificio de la estrecha válvula

mitral y permite que funcione la válvula sin aumentar apreciablemente el grado de insuficiencia mitral pre-existente.

5) Se presentan tres casos de cirugía de la válvula mitral con un sobreviviente que ha mostrado un resultado postoperatorio temprano satisfactorio. Con nuestros conocimientos presentes es indudable que se habría podido salvar a otro caso, pero el tercero probablemente estaba demasiado avanzado para que se le hubiera podido ayudar. Se describen dos casos de estrechez mitral en los que se intentó y se comenzó la cirugía pero no se la completó.

6) Opinamos que la operación de comisurotomía es muy valiosa en ciertos casos de estrechez mitral. Es indudable que se debe limitar la selección de los casos a aquellos que presentan lesiones esencialmente univalvulares en los que ha cesado toda la actividad reumática. En el estado actual de nuestros conocimientos se duda que se deba intervenir en casos de insuficiencia cardíaca congestiva aguda o crónica. Naturalmente que los resultados serían peores en ese grupo. Una de las indicaciones más urgentes para la intervención es la hemoptisis, especialmente si es grave.

7) Opinamos que la comisurotomía es preferible a una operación de desviación (anastomosis de las venas azygos y pulmonar, o abertura del séptum interauricular), porque esta última operación solamente alivia los síntomas pulmonares mediante la destrucción de uno de los mecanismos compensatorios naturales. ¿Qué se gana con aliviar los signos y síntomas de la congestión pulmonar cuando el paciente va a parar en la insuficiencia circulatoria general? ¿O si se reduce hasta tal punto la cantidad de sangre que expela el ventrículo izquierdo, por la pérdida de su mecanismo compensatorio, que se limitan aún más las actividades físicas del paciente? Empero, en un caso hipotético en el que la abertura de la válvula no redujera suficientemente la congestión pulmonar (debido quizás a la incisión muy limitada de la comisura de la válvula) no vacilaríamos en ejecutar una operación de desviación si los síntomas pulmonares amenazaran la vida del paciente. Opinamos que la hiperpresión en la aurícula izquierda en el período postoperatorio ayuda a mantener la separación de las cúspides de las válvulas después de la comisurotomía. Si se ejecuta una operación de desviación antes de la cirugía valvular, no hay duda de que existe mayor tendencia a que los bordes vivos de la comisura se unan de nuevo y reestablezcan la estenosis mitral.

8) Nos parece que la digitalización y la quinidinización preoperatorias y el empleo de procaína por la vía intravenosa durante la intervención son valiosas en ayudar la función cardíaca y en evitar las arritmias. Se administran antibióticos para evitar la infección de la herida y de las superficies cortadas de las válvulas

(infección bacteriana subaguda). Aparentemente la terapia anti-coagulante es peligrosa e innecesaria.

9) Creemos que la balistocardiografía, antes y después del ejercicio, nos ofrece la mejor medida objetiva para medir la reserva y la cantidad de sangre que expela el ventrículo.

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D i s c u s s i o n

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St. Louis, Missouri

It is thrilling to be here this afternoon and see this patient demonstrated by Dr. Bailey. I congratulate him very much indeed on his success. He was kind enough to refer to me as being one of the pioneers in this work. It was 25 years ago, in 1923, that Dr. Duff Allen and I published our first report on surgical attempts to cut the mitral valve. This was done by means of an instrument to which he referred, which, however, I am afraid he perhaps slandered a little by saying that it did not give more than a fleeting glimpse of the valve. As a matter of fact this instrument gives one very satisfactory vision, of any valve or any part of the heart with which it is in contact. It is based on the principle of a convex lens which pushes the blood away, just as one can see his finger in a glass of milk, for instance, if he pushes the finger against the side of the glass—it pushes the milk away and one can see the finger with all the lines on it and all details. That is the principle of the cardioscope which we devised. We operated successfully on a large number of dogs, making holes of various sizes in the mitral valves, depending upon what we were anxious to make. I agree fully that too large a mitral regurgitation is fatal even in the dog with a normal heart.

However, we created less degrees of mitral regurgitation in dogs many times—perhaps 50 dogs—and had them live for a long time still retaining their mitral regurgitation but able to undertake any sort of activity. We had some of these dogs live for a period of two years and then sacrificed them in order to see the condition of the heart.

Then we tried the procedure on a patient. Unfortunately, as with any new surgical procedure, the pioneers get only the patients who are the worst possible risks. Perhaps that is as it should be, there should be a certain amount of conservatism, but it seems sometimes as if our medical conferees are much too conservative about permitting the surgeon to apply a procedure which seems perfectly logical. This patient on whom we operated in 1924 was a bad risk, and she died shortly after her mitral valve had been cut. The approach was made through the auricular appendage.

I am much pleased to have this work revived by Dr. Bailey and Dr. Smithy and others, and feel certain that mitral stenosis and, in fact, stenosis of other valves, is a condition which can be corrected by surgical intervention. I don't think there is much doubt about it but I believe we are going to have to get suitable patients, we are going to have to inform our medical colleagues that it is a feasible operation and that patients must be referred, if any are going to be referred, who are not practically moribund already. On the other hand, we should not feel, necessarily, that present methods available are going to be the ideal ones; there are certainly going to be many modifications of the procedure of approach to these valves. Although I was as much thrilled as anyone here at seeing this beautiful result, I feel that we must postpone final judgment about such results until after a period of time—perhaps a year—has elapsed, because we found 25 years ago, and I think others have found since, that sometimes these valves which are cut have a tendency to heal over again and revert to their former condition. I was also much interested in the demonstration by Dr. Smithy of the great value of the intramural injection of cocaine. That is new to me, applying it within the muscle of the heart, and I think it is likely to be a procedure which will be of inestimable value in all cardiac surgery.

GORDON MURRAY, M.D.
Toronto, Canada

I wish to thank you very much for extending me the courtesy of the floor. I have enjoyed very much the papers on this subject, and my comments relate to experimental work which I did a good many years ago and reported at that time. This work was based

on the "inference" in the discussion this afternoon, namely, that division of a mitral valve may produce regurgitation, if it is a satisfactory division; and secondly, it might heal if it is divided only. Working on that assumption I thought the best idea would be to take out the diseased valve and replace it with a good one. We did that experimentally in a large group of animals in which the controls died but those with the artificial valve survived, when we had completed the operation satisfactorily.

I had hoped to postpone what I am about to say for about a year, but it would appear I am faced with saying it now. I have operated on two patients in whom I have taken out the lateral cusp of a stenosed mitral valve. Both patients were in a bad way because of mitral stenosis. A new valve was placed in each case, and they are both alive. The first one, done a few years ago, was an Indian. He disappeared later on and I don't know what happened to him. For a time, however, I know he was well, but now I can not find him as he is in the North country. The second case was operated on very recently. The patient is quite well. I do not know yet that he is benefited, nor how he is going to be, but in any case he survived and perhaps he is improved.

The method, is to take out one cusp of the valve with a punch, much as was described this afternoon. We also made a cardioscope very similar to that described by Dr. Graham, and I can assure you we can see fairly well what we want to see. It is a small field, but by shifting it around more can be seen. After having taken out the valve—we have the new valve handy—the patient very quickly begins to show some effects of regurgitation. The new valve is, I suppose, the same as you would use. A section of the cephalic vein is turned inside out so that its intima is lying in the blood stream. The palmaris longus tendon is put down the lumen of the valve to give it some substance and strength. It is then passed from before aft through the heart on the ventricular side of the site of the original valve, so that on systole it is jammed back into the opening left by resection of the valve; on diastole it floats out of the opening so that it is not an obstruction to filling of the ventricle. It seems to work satisfactorily.

HORACE G. SMITHY, M.D.

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The ramifications of this subject are of such magnitude as to prohibit consideration of the various phases in the time allotted for discussion. Therefore, I have selected one technical aspect in particular, namely, the control of cardiac arrhythmias occurring

during operation upon the valves of the heart. This can best be presented by a motion picture which will be shown subsequently.

We have performed eight operations for mitral stenosis in seven patients with two deaths. It is significant that the fatalities occurred in the second and third cases, the last five being done consecutively without serious complications as our technique gradually became better standardized. The early results in our series, while by no means brilliant, have been sufficiently encouraging to warrant pursuing this study further. We feel that the procedure can be accomplished in the future with increasingly good results and with a significant decrease in mortality.

(Motion Picture): These are excerpts selected from a complete motion picture record of the technique of experimental aortic valvulotomy in dogs developed during the past two years in the experimental laboratories of the Medical College of South Carolina. You will note in the first procedure, in which no attempt has been made to protect the animal against arrhythmias, that both ventricular tachycardia and ventricular extrasystoles were prominent features of rhythmical disturbances which occurred during placement of the purse-string suture in the cardiac apex and during passage of the valvulotome into the chamber of the left ventricle. Quite obviously, arrhythmias of this sort occurring in a human patient whose myocardium has been damaged by rheumatic fever might be the cause of an immediate fatality. As noted in the second procedure, 5 per cent procaine is being applied topically over the surface of the heart and is allowed to pool in the pericardial sac so as to bathe the epicardium generally. Observe now, the series of ectopic beats which occur following stimulation of the apex by a blunt instrument, indicating little or no protection by the topical procaine. This study has been repeated in a large series of animals; we have been unable to confirm the findings of others pertaining to the protective action of topical procaine against rhythmical disturbance.

In the third procedure, you will note that 2 per cent procaine solution is being infiltrated into the myocardium of the apex at the point where the purse-string suture will be placed and the valvulotome passed. I should like to emphasize that the procaine injection which you see on the screen is actually an intramural infiltration and not an intracardiac injection. Now watch closely and I am sure that you will agree that no ectopic beats and no evidence of tachycardia or fibrillation are to be seen during the successive series of stimulation of the infiltrated area by the blunt instrument. This procedure also has been investigated thoroughly in the laboratories and has uniformly protected successfully each animal against the occurrence of arrhythmias.

In each of our human cases in whom a ventricular approach has been selected, intramural procaine infiltration has been used as a routine. I am pleased to report that we have not encountered a serious disturbance of rhythm in any of our patients to date.

Closing Remarks

Charles P. Bailey, M.D., F.C.C.P.: You see what happens when you discuss something you don't know about! I did not know you could see very well with the cardioscope, but from the pictures in the original article I did not think it would afford good vision.

Naturally, we must wait for a year before evaluating the procedure. I believe that since the intra-auricular pressure is elevated, that when the commissures are cut, the valve will stay opened. In dogs which are permitted to survive one year after surgery there is no tendency to healing of incisions of the valve.

No one said anything about the lack of heart murmurs and precordial thrill in this girl. To my ears there are none, and most people agree with me, but there have been about 10 per cent who thought they could hear a presystolic murmur and some also a systolic murmur. I am sure it is not enough for most of you to recognize, and hope it will not increase. It is certainly remarkably different from the loud presystolic crescendo type murmur with prominent thrill which existed preoperatively.

The Importance of Continued Studies in Tuberculosis*

HERBERT L. MANTZ, M.D., F.C.C.P.

Kansas City, Missouri

Two men had just completed a golf game and were adding their scores. A second twosome approached, walked across the green and one of them asked: "How did you fellows score?" 1st Twosome: "83 and 85. What were your scores?" 2nd Twosome: "85 and 88." 1st Twosome: "Pretty close to us. We were watching you but we didn't think you were playing as we never saw you hit a ball." 2nd Twosome: "Oh we don't use balls. We know where they would go."

This very fantastic golf story is quite apropos when we think of some medical practices. The problem of using controls in therapy is not new and this is no time to go into all of its phases. I feel that it is important enough for us to give it some thought now, because we have for the first time drugs which are effective and also because surgical procedures are changing rapidly.

Progress in the treatment and control of tuberculosis moved at a comparatively leisurely pace during the past when we contrast it with the greatly accelerated tempo of these days. The inter-relationship of all scientific fields has had its effect upon the therapy of tuberculosis. In the last decade, the greatly stimulated effort in the field of antibiotics has presented new opinions and new problems to the field of tuberculosis research. New ways must be found to tackle an old problem, that is, to determine quickly and accurately the value of any pertinent discovery in the treatment of tuberculosis.

Let us look for a moment at the ways in which these answers traditionally have been found. A new form of therapy is tested by a man here and by another there; a few cases treated here and a few there; good results here, poor results there. This is essentially a trial and error approach and it does seem that there should be something better, something more orderly, which would give us a correct answer sooner. Perhaps the answer is essentially the same whether we arrive at it in one year or in 20 years. Tuberculosis therapy is measured in years, not months or days, and during these waiting years many things happen to people with

*Address of the President of the Southern Chapter, American College of Chest Physicians. Presented at Maimi, Florida, October 24, 1948.

this disease. If we can hasten the process of acquiring knowledge, we as physicians, should let nothing deter us.

Therapy in tuberculosis has always been guided by what is called "clinical judgment." This intangible factor is affected by many variables, and the most important of these is past experience. Dr. Hertzler once said that "calves suckled by the same cow were quite likely to act alike." Thus, clinicians trained with certain chest surgeons will have fewer qualms about recommending pulmonary resection than those with a more conservative background. We know about these differences of opinion and, in fact, welcome them, for they keep alive the open-mindedness and healthy discussion necessary to any science. But, we must remember that our various shades of "clinical judgment," differing as they do, are not a proper yardstick to measure the worth of any form of treatment.

In tuberculosis therapy there are many procedures which are conceded to have value. First is the basic one, bed rest. Next, are artificial pneumothorax and pneumoperitoneum, usually considered as medical procedures. Last are the surgical measures, phrenic crush, thoracoplasty and pulmonary resection. All of these are useful, but there is considerable difference in opinion as to when to use them, singly or in combination. Such divergence of thought is often disclosed in any sanatorium conference where two or more persons are free to express opinions. Such differences are good proof that we lack the carefully analyzed reliable experience necessary to develop sound judgment. It is true that we need experience to develop good judgment, but unfortunate that too often experience is gained by bad judgment.

Five years ago the tri-state area of Michigan, Wisconsin and Minnesota began a yearly conference at Pembine, Wisconsin. The most popular method of presentation has been to have a representative hospital from each state show a series of consecutive cases, at least 50 in number. Cases are chosen from one to two years back so that follow-up is possible. These three states have always been rather close in their medical relationships. If any geographical area is united in a therapy program this one should be. The surprise of the first conference was the great difference of professional opinion exhibited. To date no group has presented any study with a controlled series, and probably the chief value of such meetings has been the intensive review of cases by the individual hospitals where the cases were prepared for presentation, plus the benefits gained by observing results from other places. These conferences have been extended to other sections and have been valuable in improving clinical judgment but they have not yet provided the factual material so badly needed.

However, a start has been made to secure more facts, and because it is a significant start I should like to make a few comments about the Streptomycin Evaluation Program of the Tuberculosis Study Section of the National Institute of Health. This cooperative program began actually too late psychologically, in the case of streptomycin, because many clinicians had already formed definite clinical impressions of what the drug could accomplish and were, therefore, unwilling to let chance decide whether any particular case would or would not receive streptomycin. However, in evaluating another therapeutic agent we need not be too late as we can use this procedure before such clinical impressions, false and true, are established.

The question of the usefulness of streptomycin in the treatment of tuberculosis was first attacked by members of the Chemotherapy Committee of the American Trudeau Society, to whom the producers of the new antibiotic supplied a large amount of the drug for clinical investigation. Some of the ablest and more experienced tuberculosis clinicians in the country carried out these investigations which resulted in a number of suggestive findings. These studies provided no definitive answer as to the exact place of streptomycin in tuberculosis therapy, since there was no control group against which to measure the status of the streptomycin treated patients. It is clear, however, that the experience gained in these studies was valuable in setting up the large-scale program of the Tuberculosis Study Section for the evaluation of streptomycin. There are now three studies in progress pertaining to pulmonary, miliary and meningeal, and skeletal tuberculosis. The pulmonary study is the largest and since principles on which it is based illustrate the use of the control principles, it is sufficient to describe this alone. A detailed protocol outlining uniform procedures for all investigators was issued. Definite diagnostic criteria were established and each participating hospital submitted cases which it considered suitable for study. Cases submitted could be treated by bed rest, any type of surgery, or collapse measures. In submitting cases, the investigators said in effect: "These are cases in which I am willing to let administration of streptomycin be determined by the play of chance. I will provide any other treatment indicated to both those receiving and those not receiving streptomycin." The cases submitted are reviewed by a Selection Panel which determines the suitability of cases on the basis of the criteria established by the protocol, i.e., proved bacteriology and capable of significant improvement without streptomycin and excluding cases of minimal tuberculosis. The suitable cases are then divided by a purely random method into a treated and a control group and the hospital is bound by this decision.

If the value of a drug is completely unknown, there can be no logical objection to the establishment of a control group. Unfortunately, when this study was set up favorable "clinical impressions" of streptomycin treatment were already flourishing. Some provision had to be made, therefore, for the control patient who did so badly that it could be argued that no other therapy would be of any help, and that streptomycin might. With the controls who developed miliary or meningeal tuberculosis, the problem was simple. Past experience overwhelmingly showed that they would die without the new drug, and treatment could be started on these cases without delay. It was more difficult, however, to define the type of patient who, although not doomed with certainty, was so obviously losing out in his battle with the infection that he could reasonably be considered a "gone goose." Such patients were presented to a central "Appeals Board." The approval of this board was necessary before the patient could be treated with streptomycin.

Tuberculosis is a relatively slow moving disease. To really know what any given form of therapy is doing, it is necessary to watch a group of cases for a long time, not weeks, or months, but years. Since this is a long time job and it was obvious that paper work could develop to be an impossible chore, it became necessary to ask what we were really trying to find out, and in what order. It seemed to us that in the case of streptomycin we were trying to determine what the end result was, how two groups of patients, one receiving the drug and one not, compared at the end of the year. By placing the entire emphasis on the end result, it has been possible to request only periodic reports. If there are notable differences between the treated and the control group, then the other step must be taken; the determination of the mechanics or the significance of the changes taking place in tuberculous patients. Great stress has been laid upon uniformity and those items which are not at present susceptible of accurate measurement have not been collected, even though it is recognized that such factors as psychosomatic level undoubtedly are important in the progress of any particular patient.

Most of you have probably read the British report of a cooperative study of miliary and meningeal tuberculosis, published in the *Lancet*, April 17, 1948. An impressive body of evidence has been accumulated from a relatively small number of cases. I say "relatively" because here in America we have had much freer access to the drug, and have treated many more cases, yet when they are grouped together they justify only the most general conclusions. Why? The answer is that the British conducted a carefully regulated study in which comparable data were collected

from each case. For instance, a question arose as to the necessity of intrathecal treatment. The problem was attacked simply by withholding intrathecal streptomycin from a random group who were in other respects similar to the rest of the patients in the study. When it became apparent that these patients were faring much worse than their intrathecally treated fellows, the question was answered. This is an example of the effective use of the control principle.

With the appearance on the scene of an increasing number of new antimicrobial agents, each a "wonder drug" at first glance, we must learn to use this principle in a steadfast manner, or bog down in confusion.

The evaluation of this material is going to teach us a good deal, not only about streptomycin, but about tuberculosis, and about ways of doing cooperative studies in the future. I cannot emphasize too strongly the great stumbling block that terminology is in our present state of tuberculosis research. We must find ways of describing our clinical material so clearly that others will know exactly the kind of cases we are talking about. We must also find ways of describing the changes which take place in a year in the x-ray films of a chest so that we can know what happened without streptomycin; what happened only with streptomycin and what we failed to achieve with either.

Only meager results are available at this time, but it is interesting to note that, while the streptomycin groups appear to be markedly superior to the non-streptomycin group at the end of three months and have still an edge at six months, at nine months after beginning of treatment there appears to be practically no difference between the two groups. Reports on more cases must be accumulated before definite conclusions can be drawn.

This method of developing factual data can and should be used to evaluate some of the older but still controversial methods of therapy. When a new procedure is begun it should be tested against one which experience has valued.

Pneumoperitoneum with or without phrenic crush, and phrenic crush to supplement bed rest are two procedures always likely to provoke discussion. If we are to know which is the better we should treat series of patients concurrently, with the only variant being the procedure in question.

The use of lucite balls for extra-pleural plumbage is exciting much interest. Experience gathered from a few places ranges from uncontrolled enthusiasm to the other extreme of definite rejection of the method. With this procedure there are usually two choices. Collapse by surgery is considered advisable. We have to decide between thoracoplasty and an extrapleural operation.

Once we have decided that operation is to be done and that either one of the two procedures may be done, decide by chance and so develop two series of cases. In no other way can we come to a definite opinion. It is not scientifically sound to compare present surgical results with those of the past as surgical technique, anesthesia, preoperative and postoperative care are constantly improving. In the Veterans Administration, surgeons at first considered it necessary to use streptomycin to cover all thoracoplasty cases. Using alternate case methods they found this was unnecessary and it is doubtful if it is advisable to use it routinely in pulmonary resection. But until parallel case studies are made we will not be sure. I see no reason for not testing experimental or new procedures against tried and known ones. We can only argue about pneumoperitoneum until we have compared the procedure with bed rest by the alternate case method. When this is done perhaps skeptics may be convinced, or enthusiasts quelled.

The American College of Chest Physicians is interested in Tuberculosis Research. I believe that most of us realize the necessity of obtaining more basic knowledge of tuberculosis and we are interested in placing therapy on a better foundation. The alternate case method described should be as applicable to surgical problems as it has been in studying streptomycin. The Tuberculosis Study Section of the National Institute of Health has shown us that a cooperative study involving several different hospitals is practicable. I hope in the future that some of you will be interested in this problem, use this method of approach and find the answers to some of our questions.

In conclusion, I am reminded of a story which is all too true of many a sanatorium conference: A boat at sea ran into a severe storm. At last the captain decided to anchor, "Throw out the anchor!" he ordered. "We can't, Captain, there is no rope on the anchor." "Throw it out anyway, it may do some good."

Early Diagnosis as the Means of Tuberculosis Control

EUGENE D. RAMES, M.D.*

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Although tuberculosis has been known for many centuries, it is only in the past few decades that great strides have been made toward its conquest. This has come about largely through the development of methods by which recognition of the disease in its earliest stages can be achieved. The results are two-fold: (1) Isolation of contagious patients from individuals not contaminated. (2) Treatment of patients at a time when the greatest rate of recovery can be expected. The cases in this report may help to illustrate the effectiveness of control by the early diagnosis and supervision of students presenting evidence of having been infected with tubercle bacilli.

At the University of Minnesota, with an enrollment of approximately 27,000, the vast majority of students are in the age range of 17 to 30 years. It is in this period that tuberculosis kills more individuals annually than any other disease. The program of control at the University of Minnesota has two main objectives.

The first is the detection of the disease in any student who might be infected. The status of each entering student in relation to tuberculosis is determined. At the time of the physical examination required on admission to the University, a routine photofluorogram of the chest is made on all students. Within a period varying from one or two days, to two or three months after the initial examination, a tuberculin test, Old Tuberculin 1-1000, is applied and read in 72 hours. If the student reacts to the tuberculin, a second photofluorogram of the chest is done, and if this film indicates the possible presence of pathologic changes, a 14 x 17 inch chest x-ray film is made. If this reveals any abnormality, the student is immediately referred to the chest clinic in the Health Service, for further study.

As a result of this procedure, many of the cases of tuberculosis found among University students are of the primary infection type. The tuberculin test has proved an invaluable aid in determining the status of an individual in relation to tuberculosis. The routine photofluorogram is also of great help. There is, however, a change in the reaction to the skin test before there are significant roentgenographic findings.

*From the Students' Health Service, University of Minnesota.

The second objective in the control of tuberculosis is the supervision and rehabilitation of tuberculous patients as found among the student body. In this report are presented nine cases that represent the variety of situations that are seen in attempting to control this disease among students. With a large school of nursing, both undergraduate and public health nursing, as well as a large medical school, our total incidence of tuberculosis is higher than universities that do not have these two colleges.

Case 1: A 21 year old girl entered the school of nursing on January 2, 1945. The general physical examination revealed slight obesity; and the Mantoux test, 1-1000, was negative. In the summer of 1946 she had been exposed to a contagious tuberculous patient in the hospital. She was tested in the fall of 1946 and found to be a reactor. Six 14 x 17 chest x-ray films from the time of entrance to the University to the 19th of March 1947, were reported negative. When seen in April 1947, a 14 x 17 chest x-ray film was requested in three months. In July 1947, a 14 x 17 roentgenogram revealed a small shadow in the right lung at the level of the 4th interspace anteriorly, which was suggestive of a tuberculous lesion. Subsequently, she was x-rayed in September 1947, November 1947, and in January 1948, the changes previously mentioned remaining stationary. Three gastric lavage specimens were obtained in September 1947, but no acid fast bacilli were detected by guinea pig inoculations. The sedimentation rate was not significantly elevated. The girl has carried on her activities in the school of nursing under careful observation. There has been no progress of the disease.

This case probably represents first infection type of tuberculosis, although no tubercle bacilli were reported on gastric analysis or sputum examination. It is difficult to say without qualification that this lesion represents a primary infection in view of the fact that a period of more than one year lapsed from the time of a negative to a positive test. A primary infection may have developed, the lesion noted on the x-ray films appearing as a reinfection type of tuberculosis. It has been pointed out that it is "impossible" to locate the initial lesion in the majority of young adults who become infected with the tubercle bacillus. There is little room for doubt, however, that a definite reaction to tuberculin is an indication of the presence of tubercle formation somewhere in the body. This particular case serves to illustrate the value of doing skin tests on students of nursing and medicine at least every six months. It is only in this way that a lesion can, with certainty, be suspected as a possible tuberculous infection.

Case 2: A 22 year old male entered the University on September 19, 1946 and received an entrance physical examination. He did not react to 0.1 milligram of tuberculin, and a photofluorogram of the chest was reported as negative. In May 1947, he was still a non-reactor and routine periodic health examination was also reported as negative. A second photofluorogram of the chest at that time was negative. In October

1947, he came to the dispensary because of pain in the left anterior chest which was made worse by deep breathing. Physical examination revealed no abnormalities. Four days later he complained of marked weakness and persistence of the pain in the left chest. Physical examination revealed dullness and absence of breath sounds in the left lower lung field, and he was admitted to the hospital. The clinical impression of pleurisy with effusion was confirmed by x-ray film and he reacted strongly to 0.1 milligram of tuberculin. Pleural fluid and gastric lavage specimens did not reveal tubercle bacilli either on culture or guinea pig inoculation. In spite of this negative laboratory data, the diagnosis of tuberculosis was considered probable in view of his change in reaction to tuberculin. Inasmuch as this man was not producing any sputum, it was felt that he could safely be sent to his home for a protracted period of bed rest under the care of his physician. He has continued to improve on bed rest at home and plans to return to the University.

This case illustrates again the importance of a change from negative to positive reaction of the skin test. Although one would strongly consider tuberculosis as the most probable cause of pleurisy with effusion in a young man, it is well known that other conditions can produce this clinical picture. If the tuberculin test in this case had been made positive by previous inoculation with BCG vaccine, the likelihood of a tuberculous pleurisy might not have been given due consideration and a loss of valuable treatment time could have resulted.

Case 3: An 18 year old girl entered the school of nursing in September 1944. From October 1944, to February 1947, she was tested with tuberculin, both 0.1 and 1.0 milligram every six months and did not react. During February and March 1947, she was sent to a tuberculosis sanatorium for a part of her course of study. A 14 x 17 x-ray film of the chest in March 1947, was interpreted as negative. In the early part of June 1947, 0.1 milligram of tuberculin produced a strong reaction. An x-ray inspection of the chest at that time revealed an infiltrative lesion in the right cardiophrenic sinus with linear infiltration from this area towards the hilus of the right lung. The roentgenologist's report stated that the lesion strongly suggested either a lymphoblastoma or a mediastinal Hodgkin's disease. The evidence in favor of tuberculosis, however, was heightened by the change of the tuberculin reaction from negative to strongly positive within a 6 month period. The final diagnosis was tuberculosis, probably of the primary infection type. The patient was hospitalized and acid fast bacilli were demonstrated in gastric lavage specimens on two occasions.

Here again, the change of reaction from a negative to strongly positive is of inestimable value in the establishment of an early diagnosis. The primary impression of the x-ray department had been lymphoblastoma or possibly Hodgkin's disease with tuberculosis as a third possibility. If the tuberculin test is discarded as a diagnostic procedure, there is a risk of infectious cases remaining undiagnosed until their sputum becomes positive for tubercle

bacillus and the disease has advanced to the point where a much longer period of treatment is indicated.

Case 4: An 18 year old male entered the University in September 1946. There was no personal or family history of tuberculosis. A photofluorogram of the chest then and another in May 1947 were reported as negative. In this case, there is no record of whether he had had a previous tuberculin test at the time of his entrance to the University, and for some unknown reason he was not tested after admission. In December 1947, he had an x-ray picture done at the time of the chest survey in St. Paul, Minn. An infiltrative lesion in the left subclavicular area was found. Subsequent films in January 1948, again showed the lesion and it was concluded the infiltration was due to atypical pneumonia, infected lung cyst or abscess, with the possibility of a reinfection type of tuberculosis. Stereoscopic films a short time later revealed evidence of cavity in the subclavicular region on the left. It is likely that the lesion was present six months previously, which was a short time after the photofluorogram of the chest had been reported as negative. The basis for this statement is the fact that a cavity with a wall as thick as the one seen rarely develops in less than six months. Tubercle bacilli were demonstrated in the sputum. The diagnosis of advanced pulmonary tuberculosis was made. The student withdrew from school and arrangements were made for hospitalization.

If a tuberculin test had been done when the patient entered the University, a more careful observation of the student would have taken place, and the lesion, perhaps, would have been discovered at an earlier stage.

Case 5: An 18 year old girl entered the school of nursing in January 1945, at which time she did not react to 1.0 milligram of tuberculin. Subsequent tests applied every six months were negative until May 1947, when she reacted to 0.1 milligram of tuberculin. Since that time, this girl has had chest x-ray films approximately every three months which have revealed no evidence of tuberculosis.

This patient, then, represents the most common response of the young adult who was a non-reactor and subsequently becomes exposed to and infected with tubercle bacilli. In this respect the response is identical to that seen in infants and children who are similarly exposed.

Case 6: An 18 year old girl entered the school of nursing in October 1942. The family history and past history of the patient revealed no tuberculosis. The physical examination showed no significant physical defects, and she did not react to 0.1 milligrams of tuberculin. Subsequently, from March 1944, until May 1945, she was given tuberculin tests, 1.0 milligram of tuberculin every six months, but did not react. After completion of her training on a large tuberculosis service, a tuberculin test was applied in the latter part of January 1946, and found to be strongly positive. X-ray films of the chest in February 1946, were reported as negative. However, in that month she reported to the dispensary because of pain in the left side of the chest which had been

present for two weeks. This pain was made worse by deep breathing. Examination on this first visit revealed no pulmonary pathologic changes. However, the pain persisted for a period of about 3 weeks, and in March 1946, she was found to have a temperature of 100 degrees F. She was admitted to the hospital and a series of x-ray films were taken. On March 25, 1946, a chest roentgenogram showed a mediastinal mass, areas of increased density in the left lung field above the diaphragm and in the middle portion and the left hilar shadow was noted to be greatly enlarged. Five days later, a chest x-ray film showed the same findings, with the conclusion that sarcoidosis was the most likely diagnosis.

On April 6, 1946, another chest x-ray film showed findings which caused question of a primary type of tuberculosis of fairly extensive nature to be raised. The patient was not producing any sputum, but three gastric lavage specimens produced tuberculosis in guinea pigs. After two weeks of hospitalization at the Students' Health Service, the patient was discharged to her home on a regime of strict bed rest under the care of her private physician. It would not seem too illogical to surmise in this case that had it not been for the change in the tuberculin reaction from negative to positive, the diagnosis of tuberculosis might not have been made until it became apparent that there was considerable spread of the process.

Case 7: This girl entered the University in September 1945, at the age of 20 and gave a history of having been a reactor to tuberculin since 1941, at which time one Indian boy and two other students in her high school class developed active tuberculosis. Two of these cases were known to be contagious. In the fall of 1941 she developed pleurisy with effusion. Inoculation of pleural fluid into a guinea pig resulted in tuberculosis in the animal. She was in bed at home for about one year and remained out of school for two years.

X-ray studies of the chest at the time of admission to the University revealed a rectangular shaped homogeneous shadow lying laterally in the lower lung field which was thought to be a markedly thickened pleura. Comparison with films taken elsewhere in 1942 and 1943 revealed the same shadow which confirmed this impression. She has had chest x-ray films at regular intervals throughout her stay at the University, the most recent one being in February 1948, and there has been no change in the appearance of the chest.

This case is an excellent example of the development of tuberculosis. Earlier, in the very year in which she contracted the disease, she had been declared the 4H Health champion at the Minnesota State Fair when she was a non-reactor to tuberculin. The sequence of events is important. There is a history of known exposure with subsequent reaction to tuberculin. Within one month after the test had been made, she developed the tuberculous effusion.

Case 8: A 28 year old graduate nurse entered the school of public health nursing in September 1947. She reported a previous tuberculin reaction. When a photofluorogram of the chest was taken at the time of her entrance examination, a repeat examination was requested by the x-ray department because the first one was unsatisfactory. The second

photofluorogram of the chest was done on December 2, 1947, and revealed some linear densities in the right lung. Subsequent history revealed that she had a mild cold in September of 1947, accompanied by slight pain in the right side of her chest on deep inspiration. This subsided in a few days. She continued to feel well until December 2, 1947, when she had a recurrence of the pleural pain. Because the pain in the thorax persisted, she returned to the dispensary on December 5th. Again physical examination revealed no chest pathology. On December 9th, physical examination revealed definite evidence of pleural effusion and she was admitted to the hospital. A 14 x 17 chest x-ray film confirmed the presence of pleural effusion with adhesions and pocketing on the right, but no parenchymal lesions could be clearly defined. A tuberculin test was applied and found to be strongly positive in 48 hours. Pleural fluid was aspirated and inoculated into guinea pigs but resulted in development of no tuberculous lesions. She remained in the hospital for a period of 26 days during which time the amount of fluid in the right base gradually decreased until at the time of discharge the lung fields on both sides appeared clear by x-ray. During hospitalization she ran a daily temperature elevation and the sedimentation rate was consistently and significantly elevated. She was transferred to another hospital for further treatment.

This case points out the importance of periodic observations for the development of a tuberculous effusion in a known reactor. This, of course, becomes doubly important in the case of a nurse or a medical student.

Case 9: A 22 year old man entered the University in September 1946, at which time he stated that he was a reactor to tuberculin. A photofluorogram of the chest at that time was negative. On September 28, 1947, he was admitted to the Students' Health Service Hospital because of pulmonary hemorrhage of two days duration. Further history revealed that he had had a "cigarette cough" for about a year and a half. This, he had noted, was worse in the morning and productive of a moderate quantity of thick, foul-smelling sputum. Approximately six months prior to admission to the hospital, he had reported to the Minneapolis Public Health Center because of hemoptysis. No evidence of tuberculosis was found at that time after careful roentgenography, laboratory studies and physical examination. On May 22, 1947, a photofluorogram of the chest at the Students' Health Service once again was negative.

In view of the history, a tentative diagnosis of bronchiectasis was made and an x-ray film done on September 28, 1947, showed infiltration of the right base which was interpreted as a pneumonitis superimposed on a pre-existing bronchiectasis. Repeated sputum examinations were done and were reported as negative until October 3, 1947, at which time large numbers of tubercle bacilli were found in a specimen of sputum. On October 9, 1947, another chest x-ray film was made which revealed a probable bronchogenic dissemination of tuberculosis throughout both lungs. It was felt that streptomycin therapy was indicated and arrangements were made for admission to the Veterans Hospital, where he is making a very good recovery.

This case serves to illustrate again the importance of keeping the possibility of tuberculosis infection ever present in our minds.

COMMENT

The advantages to the patient and to the community, of making the diagnosis of tuberculosis at the earliest possible time, are self-evident. The only way, at present, to eliminate this disease is by the diagnosis and treatment of the very early tuberculous patient before he becomes contagious. If he becomes contagious, he should be isolated as long as he is capable of transmitting the disease to others. This is as true of communities and states as it is of the University, for certainly universities represent small communities. With the advent of the routine photofluorogram, a valuable method was added to our fight against this disease. However, as the above cases illustrate, the tuberculin test is an important part of any tuberculosis control program. The importance of the routine testing of all University students cannot be overemphasized. It is equally desirable in the general practice of medicine, to test patients routinely, unless they have previously been found to react to tuberculin.

In his very excellent report of the situation among college students in Texas, Johnson has set forth the general objectives of a college control program as being three in number: 1) to determine the status of each student upon admission; 2) an annual tuberculosis survey of the resident student body; and 3) medical supervisory control of all rehabilitated tuberculous patients. At the University of Minnesota the first and third of these objectives have been put into practice. The second is at present applied to students of nursing and medicine.

SUMMARY

The result of conducting a fundamental tuberculosis control program is a reduction in the incidence of this disease. In the past six months, in this "fair-sized community" of students, there have been found only about 20 new cases. The majority of these are at a very early stage and, for the most part, are now under treatment. Certainly, until there is a method developed that will insure true immunity to this disease, the use of the Mantoux test should be continued as it is the one diagnostic procedure which will tell those individuals who have been infected with tuberculosis and therefore need careful supervision.

RESUMEN

El resultado de llevar a cabo un programa fundamental para el control de la tuberculosis es la reducción en la frecuencia de esta enfermedad. En esta colectividad bastante grande de estudiantes sólo se han descubierto 20 nuevos casos en los últimos

seis meses. La mayoría de ellos se encuentran en un período muy temprano y la mayor parte están ya bajo tratamiento. Seguramente que hasta que se desarrolle un método que asegure una verdadera inmunidad contra esta enfermedad, se debe continuar el uso de la prueba de Mantoux, pues este es el único procedimiento diagnóstico que indica cuales son los individuos que han sido infectados con tuberculosis y que, por consiguiente, necesitan cuidadosa vigilancia.

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Diagnosis of Cancer of the Lung by the Cytologic Method*

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The application of the fixation and staining technique developed by one of us (Papanicolaou)^{1,2} in the study of sputum for cancer cells was first used by us June 22, 1945. The material was procured from a patient whose symptoms were those of a man who was discharged from the United States Navy in April 1945 as a psychoneurotic. His routine chest plate was reported as negative. He had a chronic, so-called "tobacco" cough, anorexia, insomnia, restlessness, nervousness and weight loss. On June 5th, 1945 he coughed up a small quantity of blood and a chest x-ray examination revealed an infiltrative lesion in the right upper lobe with nodes along the right mediastinal border. Bronchoscopy and bronchial washings were negative. Sputum smears showed typical cancer cells. Subsequent exploratory operation revealed an inoperable bronchogenic carcinoma (Figures 1, 2 and 3).

Since the above date, over 1,300 cases have been studied. The specimens were procured primarily from patients of the New York Hospital and the Memorial Hospital. A monograph is now under preparation in which a description of the cytologic findings and a statistical analysis of the diagnostic accuracy of this method will be given. In a tabulation of 298 cases already reported in the American Journal of Public Health,³ the accuracy was approximately 95 per cent for the positive reports (Classes IV and V)[†] and 85 per cent for the negative (Classes I and II). Of the cases reported as suspicious (Class III), approximately 50 per cent proved subsequently to be positive.

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†Smear reports have been given on the basis of the following classification:

Negative,

Class I. Absence of atypical or abnormal cells.

Class II. Atypical cells present but without abnormal features.

Suspicious,

Class III. Cells with abnormal features suggestive but not conclusive for malignancy.

Class IV. Cells and cell clusters fairly conclusive for malignancy.

Class V. Cells and cell clusters conclusive for malignancy.

The technique of preparing and staining smears from sputum may be summarized as follows:

Sputum is expectorated directly for examination or put immediately into 70 per cent alcohol, in order to secure a good fixation and preservation of the cells. It is then spread on slides which have been previously coated with a thin film of Mayer's albumen. The smears are immersed, while moist, in equal parts of 95 per cent alcohol and ether, for at least thirty minutes. They are then stained in hematoxylin, OG6 and EA65, following procedure No. 267.^{1,4}

Aspirated bronchial secretions and bronchial washings are mixed immediately with an equal volume of 95 per cent alcohol and ether

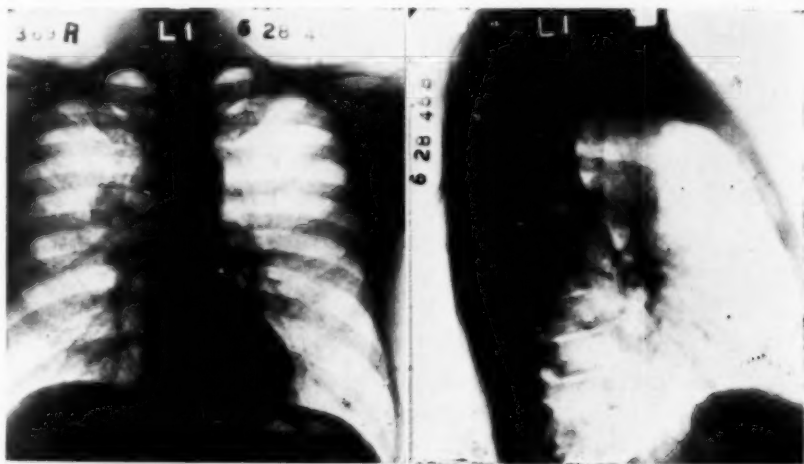


Figure 1a and 1b, Case L1: Photographs of x-ray plates showing enlarged nodes in right hilar region.

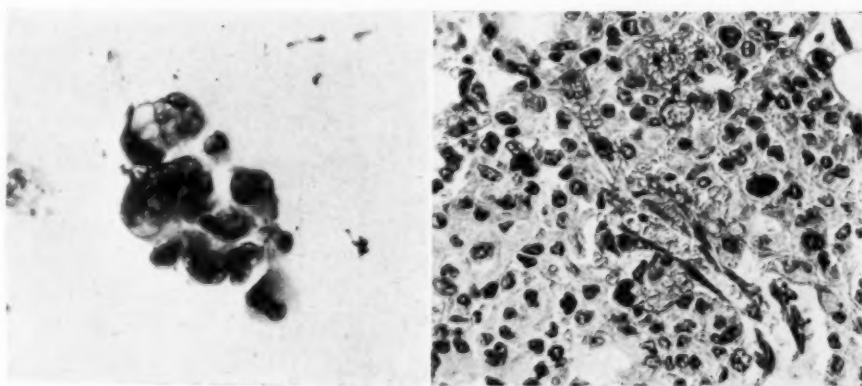


FIGURE 2

FIGURE 3

Figure 2, Case L1: Sputum smear. Cluster of malignant cells. Photomicrograph X285.—Figure 3, Case L1: Section of node from hilus of right lung showing bronchiogenic carcinoma. Photomicrograph X285. (Courtesy of the Pathological Laboratory of St. Luke's Hospital).

and centrifuged for thirty minutes at medium speed. Smears are made from the sediment, fixed promptly in equal parts of 95 per cent alcohol and ether and stained by the same method as the sputum smears.

During the early phase of the work, most of our examinations were limited to a single sputum specimen. Repeat sputum specimens and aspirated bronchial secretions or washings were made available to us in a relatively small number of cases. We now request repeat specimens as well as aspirated bronchial secretions or washings in all cases in which smear findings have been negative or suspicious. In some instances, more particularly in the early cases the number of exfoliated cancer cells may be small and the chance of missing a positive case greater if only one specimen of either type is examined.

The clinical value of the cytologic method is demonstrated by the fact that in many instances of pulmonary neoplasm, it furnished the primary diagnosis or the only preoperative histologic positive evidence. Over twelve pneumonectomies have been performed at the Memorial Hospital and the New York Hospital with a Class V smear report as the only positive preoperative histologic evidence to justify surgery.

The diagnostic value of the cytologic method is exemplified by the following two cases:

Case 1: D. W., L959, Male, 50 years old.

Symptoms: (1) Virus pneumonia, August 1947. (2) Recurrence, December 1947. (3) Slight cough. (4) Pure culture, *Monilia*, January 1948.

Physical Examination: (1) Moist rales, right posterior lateral base. (2) Old right apical tuberculosis.

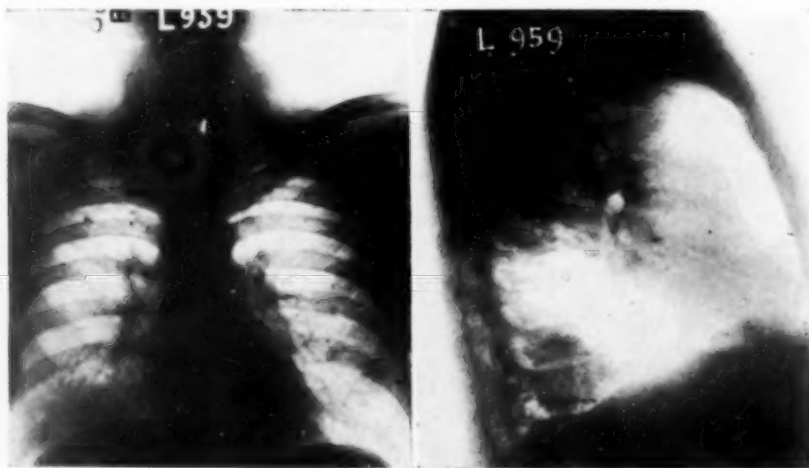


Figure 4 a and 4 b, Case L959: Photographs of x-ray plates showing infiltrative process in base of right lung.

X-ray Report: Infiltration in right lower lung fields. Findings seem most consistent with an inflammatory process (Figure 4).

Bronchoscopy: Entirely negative.

Bronchial Washing Smear (Figure 5) reported as follows: "Conclusive evidence of a malignant neoplasm. Malignant cells are numerous. Class V."

Pneumonectomy was performed. After the operation the smear became negative.

Gross Specimen: Basal portion of lower lobe is almost completely replaced by large, moderately firm tumor mass.

Section of lung (Figure 6): Carcinoma of lung Grade II. Peripheral bronchiolar type, having papillary and pseudoglandular features.

Case 2: W. M., L593, Male, 56 years old.

Symptoms: (1) Chest pain for 8 months. (2) Chronic cough. (3) Sputum, profuse. (4) Weight loss of 14 pounds.

Physical Examination: Suppressed breath and voice sounds in right lower chest.

X-ray (Figure 7): "An endobronchial tumor as well as bronchiectasis must be considered."

Bronchoscopy: Entirely negative.

Bronchial Washings (Figure 8): "Conclusive evidence of a malignant neoplasm, most likely a bronchogenic carcinoma. Class IV-V."

Pneumonectomy was performed.

Gross Specimen: Infiltrating tumor mass is seen at the bifurcation of the right lower lobe bronchus.

Section (Figure 9): Bronchogenic epidermoid carcinoma Grade III. The extrapulmonary nodes show no tumor.

Diagnosis by the cytologic method is based on the identification of malignant cells which may appear either singly or in clusters. Small fragments of tissue in the form of cell clusters are found frequently in cancer smears. The criteria are, therefore, cytologic as well as histologic. Of the cytologic criteria, the most pathog-

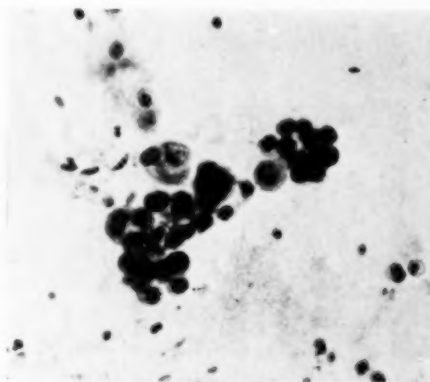


FIGURE 5

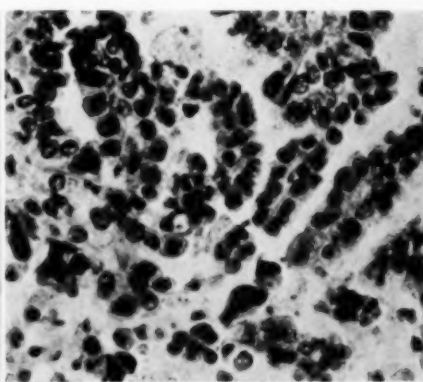


FIGURE 6

Figure 5, Case L959: Sputum smear. Cluster of malignant cells. Photomicrograph X285.—Figure 6, Case L959: Section of tumor of right lung showing carcinoma of lung grade II. Photomicrograph X285. (Courtesy of the Pathological Laboratory of Memorial Hospital).

nomonic are those related to changes in the size, form and consistency of the nucleus. In certain types of carcinomas, as the epidermoid, cancer cells display striking structural abnormalities, which greatly facilitate their detection. Of the histologic criteria, the most significant are the irregularity in pattern, the anisocytosis and anisocaryosis and the crowding of the cells within each group.

In infectious processes, such as pulmonary tuberculosis and pneumonia, exfoliated cells may show atypical features but these are in no way comparable to those found in carcinoma cells. One condition in which exfoliated cells may appear in clusters

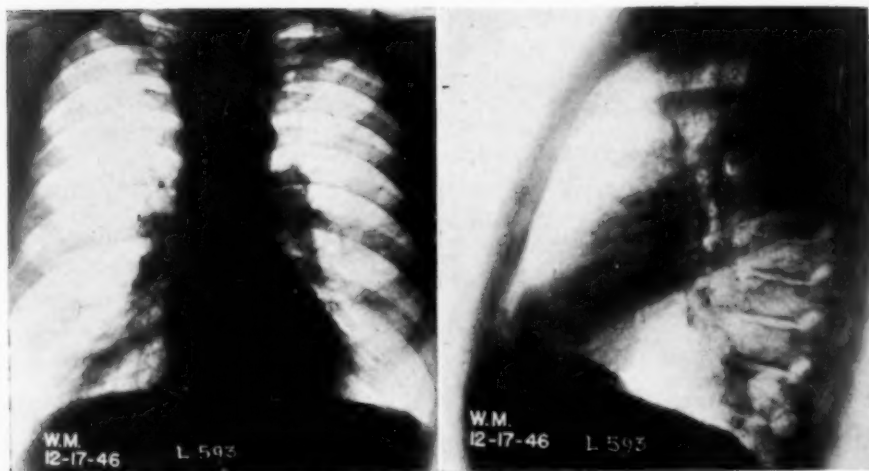


Figure 7 a and 7 b, Case L593: Photographs of x-ray plates showing infiltrative process in base of right lung.

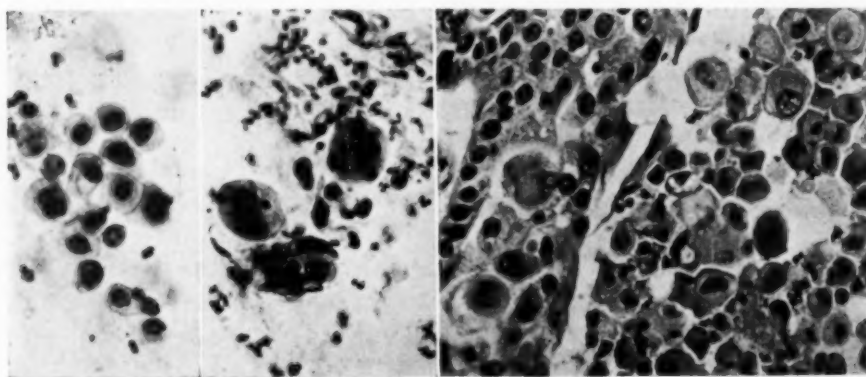


FIGURE 8

FIGURE 9

Figure 8, Case L593: Sputum smear. Cluster and group of malignant cells. Photomicrograph X285.—Figure 9, Case L593: Section of tumor of right lung showing bronchiogenic epidermoid carcinoma grade III. Note exfoliated cells on right half of section. Photomicrograph X285. (Courtesy of the Pathological Laboratory of Memorial Hospital).

suggestive of a neoplastic type of exfoliation is bronchiectasis. Because of such cell groups, false Class IV positive reports have been given in the first three cases of this type. We now feel that the atypical cells found in bronchiectasis can be differentiated from true malignant cells by the absence of nuclear abnormalities and by some distinctive structural characteristics. Oat cell carcinomas present a greater difficulty in diagnosis because of the smallness of the cells which may be easily overlooked unless found in sizable groups. Epithelial pearls when found in a sputum or an aspirated bronchial secretion always raise strong suspicion of a malignant neoplasm. Dense groups of lymphocytes are also highly suggestive. Thus far, we have noted such groups only in a small number of positive cases.

In the past three years, we have come to believe that the cytologic method is of definite value as an aid in diagnosing cancer of the lung. Evaluation of the advantages of this method to the clinician may be summarized as follows:

It helps in the diagnosis of obscure cases. In some instances where bronchoscopy and aspiration biopsy were negative and the x-ray examination inconclusive, a positive sputum report revealed the true nature of the lesion.

It aids in the earlier diagnosis of pulmonary neoplasm. At times, the sputum report has been positive from a day to weeks before any other histologic evidence of cancer was obtained. It is, therefore, of value for screening purposes in cancer detection clinics.

It tends to accelerate the diagnosis and to increase the percentage of operable cases. This is of particular importance since it enhances the chance of cure of these patients through surgical intervention. The poor results with x-ray therapy are only too well recognized. The gratifying results of early surgery are generally well appreciated.

It is particularly useful in establishing a diagnosis of carcinomas of the superior sulcus, so-called Pancoast's tumors. Tumors in this part of the lung are inaccessible to the bronchoscope. When x-ray findings are meagre, bronchial washings from both right and left main bronchi may decide the issue. Recently we had such a case in which the washing from the right main bronchus was positive (Class V) whereas the reading from the left was negative (Class I).

Because of its technical simplicity and low cost, repeated specimens can be obtained. This makes it particularly advantageous in postoperative and postirradiation follow-up.

CONCLUSION

We wish to emphasize the difficulty in interpreting smears and the need of adequate training for laboratory men who wish to

undertake this type of work. The value of the method depends largely on the training and proficiency of the person interpreting the smears.

CONCLUSION

Deseamos recalcar la dificultad de interpretar los frotos y la necesidad del entrenamiento adecuado de los médicos de laboratorio que deseen llevar a cabo esta clase de trabajo. El valor del método depende en gran parte del entrenamiento y la habilidad de la persona que interprete los frotos.

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D i s c u s s i o n

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This is an important and timely subject, because carcinoma of the bronchus is unquestionably on the increase. Whether this is real or apparent is beside the point; there are more patients with carcinoma. Surgeons are treating it satisfactorily but the difficulty lies in getting patients to them early so that extirpation of carcinoma still can be done. Our attention was directed forcibly to this several years ago, when Dr. Herbut and I checked the cases of carcinoma of the bronchus that we had diagnosed by bronchoscopic biopsy and then checked to see how many the surgeon was able to treat. This number was small. Obviously there is something wrong. We felt that with the high percentage of positive bronchoscopic biopsies (reports in medical literature vary from 60 to 85 per cent), there should have been more for surgical treatment. The difficulty lay in the fact that a majority of patients are diagnosed too late and a positive bronchoscopic biopsy merely meant that the carcinoma was in a larger bronchus. We therefore concluded that something more should be done to aid in diagnosis particularly in those lesions which could not be visualized bronchoscopically, namely, upper lobe lesions and lesions

in the periphery of the lung which were beyond the view of the bronchologist. With the excellent work of Dr. Papanicolaou in the diagnosis of uterine carcinoma we believed here was an opportunity since carcinoma of a bronchus is bronchogenic and cancer cells should be exfoliated and should appear in bronchial secretions. We started with a study of bronchial secretions of known bronchogenic carcinomas, and found that cancer cells appeared in variable numbers and could be identified.

Secretions are secured bronchoscopically from the bronchus that presumably is draining the lobe in which the roentgenogram reveals a shadow. Since there often is little or no sputum in early cases of carcinoma we were confronted with the problem of securing secretions bronchoscopically in one who had no increase in secretions. Various means were attempted but the majority of them were not satisfactory, and now we instil normal saline solution into the suspected bronchial subdivision, reaspirate the material and submit that to the laboratory for cytologic study. One often must employ posture, for example, with an upper lobe lesion the patient is placed on that side after the bronchoscope is inserted. With the aid of a curved aspirator for instillation of salt solution, about 2 or 3 cc. are instilled and then reaspirated. Since that has been done our percentage of positive findings in lesions around the corner has increased.

It is of course important to pick up early lesions. Late diagnosis is inconsequential and only of didactic interest.

(Slides then were shown of five patients, all of whom had early pulmonary lesions with slight symptoms, roentgen findings that were only suggestive of neoplasm and negative bronchoscopic findings. Cytologic studies revealed carcinoma and all were treated surgically).

In a recent study of our results which cover over 1,000 patients there were found 205 cases of carcinoma of the bronchus. Of these a positive bronchoscopic biopsy was secured in 76 (37.5 per cent); stenosis or deformity and fixation of a bronchus observed bronchoscopically in 46 (22.4 per cent); positive diagnosis by cytologic study of bronchoscopically removed secretion in 185 (90.2 per cent). This study therefore gave a 32.6 per cent margin of positive biopsies to the cytologic method in cases that were negative bronchoscopically. This group represents an important one for many of these represented early cases and amenable to surgical treatment.

I care not how you make diagnosis; the important thing is, make it early; do not wait until there are roentgen evidences of bronchial obstruction, copious sputum and palpable nodes and other evidences of advanced disease. We must make the diagnosis early. If you prefer to examine the sputum well and good. We

prefer bronchoscopy and believe the method of cytologic study of bronchoscopically removed secretion has contributed enormously at our clinic.

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I would like to mention a practical aid. If a patient has sputum which is purulent or tenacious and loaded with bacteria it may be difficult to find malignant cells. In a few of these patients we have given iodides and a week's course of penicillin. Following the decrease in the amount of sputum and a change in its character we have been able to find malignant cells in a few patients. Dr. Cromwell's remarks concerning additional specific training for physicians and technicians must be stressed in this field. It is well to keep in mind that there are courses in cytological diagnosis now being given in the different parts of the country.

Closing Remarks

Henry A. Cromwell, M.D.: After hearing these papers and discussions, I believe we all have a better idea of how to diagnose lung cancer earlier. I feel that the use of this method inspires one to greater effort in cancer detection. Dr. Clerf brought out some pertinent facts and gave us some solid advice. We owe him a debt of gratitude for his contribution to this meeting.

It is a well known fact that treatment can only be as good as the diagnosis. The first prerequisite to early diagnosis of cancer is to suspect its presence. Early diagnosis is mandatory if one is to treat cancer with the idea of cure. The delicate structure of the lungs prevents intensive irradiation therapy as is used in other parts of the body. This leaves surgery the only sincere approach towards a cure. Since Dr. Evarts Graham performed the first pneumonectomy in 1933 great hope has been entertained regarding the treatment of this hitherto rather hopeless condition. We do not have here a sure-fire single diagnostic procedure. Rather, we have an added tool for use in diagnosis. Dr. Papanicolaou in his simple straight-forward manner has demonstrated what can be expected from the cytologic method of diagnosis and you have today seen the preliminary results. The success or failure of this method depends on us as well as on the cytologist. First it is up to us to suspect the presence of cancer and procure adequate specimens for smears, then follow up the results with good sound judgment.

A lot more has to be learned about this work and many precautions have to be observed. One of these is that one should not depend on a single negative or positive report. Repeat specimens are urged. One cannot feel sure there is no cancer present just because the sputum, aspiration biopsy, or bronchial washing is negative. We have had cases in which at one time or another any one of these tests was negative; that is, none of them is always positive in the presence of cancer. Why a positive sputum obtains at times with a negative bronchial washing, or vice versa, is not clear. Cells may be exfoliating yet not be present in the specimen at a particular time. We do not know why this happens. It may occur because the smear is from the oral cavity and not from the bronchial tree. Statistics reveal that 10 per cent of lung cancers are potentially operable when first diagnosed. Only 60 per cent of these are likely to be surgically resectable. This is a low percentage. We are interested in trying to screen patients with early symptoms, particularly males. The percentage of bronchogenic carcinoma in the male is high—the literature states about 75 per cent. I think our series will run more nearly 90 per cent in males and 10 per cent in females. Here we have a little to work on as far as sex is concerned. Then there is the factor of age. We must watch males from say 40 to 55 years of age particularly. Below and above these ages cancer of the lung occurs in decreasing percentages.

Fixation and proper staining of slides are of prime importance. A pathologist may be extremely proficient but when it comes to sputum, or bronchial washings, or aspirates, he needs special training to fix and stain the smears and to recognize exfoliated cells.

By the use of the cytologic method we can expect earlier diagnoses and an increase in the number of cured cases by prompt surgical intervention.

One Half Gram of Streptomycin in the Treatment of Pulmonary and Extrapulmonary Tuberculosis

Report of 120 Cases*

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Following the work of Schotz, Bugie and Waksman¹ on the discovery of the inhibitory effect of streptomycin on gram negative organisms, Feldman, Hinshaw and Mann² reported the marked suppressive effect of streptomycin on tuberculosis in guinea pigs. Youmans and Carter³ confirmed this by testing streptomycin on tuberculosis in mice.

Keefer, Blake, Lockwood, Long, Marshall and Wood Jr.,⁴ in a review of the use of streptomycin in all types of infections in humans, reported the response of cases of tuberculous laryngitis, draining sinuses, osteomyelitis and the genito-urinary tracts. Although the dosage was not clear, it appeared that over 1 gram daily was used. Cook, Greene and Hinshaw⁵ were encouraged with the use of streptomycin in the treatment of renal tuberculosis, as were Hinshaw, Feldman and Pfuetze⁶ with pulmonary and extrapulmonary tuberculosis.

Zenkel, Flippin, Nichols, Wiley and Rhoads,⁷ using 0.5 gram dosages of streptomycin intramuscularly, found that the highest blood level was reached at 3 to 4 hours. Anderson and Jewell⁸ did not encounter toxic effects on 0.5 gram given every 3 to 4 hours; whereas Heilman, Heilman, Hinshaw, Nichols, and Herrell⁹ showed that streptomycin could be given intramuscularly, intravenously, subcutaneously, intrathecally, orally and by nebulization with varying toxic results.

With this background of literature and a few of our own preliminary cases, in March 1947 the staff† of the Missouri State Sanatorium decided to initiate a series of cases using 0.5 gram daily with 0.25 gram injections at 12 hour intervals for 4 to 6 months. Our plan was to compare results with those of investigators mentioned who had used a higher dosage. Although our laboratory was not able to run sensitivity and blood levels, we

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believe as did Hinshaw¹⁰ that the clinical test is the one test of prime importance. With the theory of subjecting the infection to a higher concentration of the drug the first few days, we divided one gram of streptomycin daily into 12 hour dosages for the first week and followed with the 0.5 gram schedule. One hundred twenty successive cases that had finished their courses and had been roentgenologically unchanged or progressively worse for the previous 3 to 6 months were chosen for this report. Their ages ranged from 8 to 75 years. Thirty-two cases were receiving either pneumoperitoneum or pneumothorax treatments. Of the 79 females and 41 males, 106 were caucasian and 14 were negroes. Ninety-one cases were classified as far advanced, 24 as moderately advanced and 5 as minimal according to the National Tuberculosis Association classification. The 5 minimal cases were treated because of either draining tuberculous sinuses or osteomyelitis. Several of the cases were terminal and several had fibrotic disease, but were treated for our own evaluation of streptomycin in this type of disease (Table I).

All but 6 patients had marked decrease of cough and expectoration and an increase in appetite. Of the 64 cases with an elevation of temperature, 31 had from 99 to 100° F., 15 from 100 to 101° and 18 above 101° F. Forty-three (67.2 per cent) returned to normal, 8 (12.4 per cent) returned to 99°, and 13 (20.4 per cent) had no change whatever (Table II). Ninety-nine cases could be evaluated as to weight. Those that did not gain weight even though of "normal" weight were classified in the "no-gain" or "lost-weight" column. Seventy (70.7 per cent) gained weight (1-5 lbs., 16.2 per cent; 5-10 lbs., 24.2 per cent; 10-20 lbs., 30.3 per cent), and 29 (29.3 per cent) had no change or lost weight.

Laboratory Observation: One hundred cases had abnormal sedimentation rates (Cutler method 2-10 mm. per hour normal value). Twenty-six (26 per cent) returned to normal, 36 (36 per cent) decreased from 1 to 14 points although still above normal, and 38 (38 per cent) had no change (Table III). Eighty-seven cases were evaluated as to sputum conversion (by smear or concentrate). Thirty-nine (45 per cent) were converted, 3 (3.3 per cent) changed from consistently positive to alternately positive and negative, and 45 (51.7 per cent) remained positive. Several of the cases that had sputum conversion during streptomycin are now positive after the course was finished. One of the most interesting results first noticed was the cessation of hemorrhage or bloody sputum after the first few days treatment of streptomycin. Fisher, Fishburn and Wallace¹¹ reported that in 53 per cent of their cases hemoptysis disappeared.

Exudative: There were 36 cases of roentgenographic exudative

infiltration, 2 of which also had coexisting fibrotic disease. Ten cases were negroes. Nineteen cases were receiving either pneumoperitoneum or pneumothorax treatment with no response. Sixteen (44.4 per cent) had marked improvement or disappearance of the exudative infiltration in from 1 to 6 months. In 2 of these cases the collapse therapy may have been partially responsible. Seven (19.4 per cent) cases were moderately improved and 13 (36.2 per cent) had no improvement. Ten cases had converted sputums and 2 were changed from consistently positive to alternately negative and positive. Our results are not as favorable as the Veterans Administrations Groups (Table IV).

Cavities: Thirty-two cases had roentgenographic cavities. Twelve (37.5 per cent) were healed or lost to view, 6 (18.8 per cent) were smaller, and 14 (43.7 per cent) were not improved or larger. Ten of the 12 healed cases were judged to have exudative infiltration before the course of streptomycin, and 2 of the 12 were judged to have a moderate amount of both exudative and fibrotic disease. There was no response to streptomycin in cavities of cases of fibrotic disease. In the "no-improvement" group, 7 had predominantly fibrotic disease, 6 exudative disease and 1 both types. All but 2 cases received streptomycin from 4 to 6 months. One of these received streptomycin for 61 days, had fibrotic type of disease and had no change; and 1 received streptomycin for 90 days, had exudative disease and had moderate decrease in the size of the cavity. Ten of the 12 "closed-cavity" cases were receiving pneumothorax or pneumoperitoneum treatments with no im-

TABLE I
Age Range in Years

| Age | 8 | 15-19 | 20-29 | 30-39 | 40-59 | 60-75 |
|--------------|---|-------|-------|-------|-------|-------|
| No. of Cases | 3 | 10 | 43 | 30 | 11 | 120 |

TABLE II
Clinical Results

| | | TEMPERATURE | | | | WEIGHT | |
|--------------------|-----|-------------|------------------------|---------------------|------------------|-----------|--------|
| | | Total No. | Total number decreased | Decreased to normal | Decreased to 99° | Total No. | Gained |
| Mo. State San. | No. | 64 | 51 | 43 | 8 | 99 | 70 |
| | % | | 79.6 | 67.2 | 12.4 | | 70.7 |
| V. A. ⁴ | No. | 160 | 117 | 76 | | 223 | 188 |
| | % | | 73.1 | 47.5 | | | 84.3 |

provement in the status of the cavity. Twelve of the 32 cases having cavities had converted sputums; 3 of the converted cases still had cavities. Nine of the "closed-cavity" cases had converted sputums. Our results, as compared with the Veterans Group (Table V), are favorable.

Atelectasis: We have been impressed with the use of streptomycin in cases with atelectasis, especially if present in lungs receiving some type of collapse measures. We believe that responses in those cases are probably due to dealing of endo-bronchial tuberculosis of the more distal bronchi. Of the 5 cases studied, 3 cleared

TABLE III
Laboratory Results

| | | SEDIMENTATION RATE | | | SPUTUM | |
|--------------------|-----|--------------------|------------------------|------------------------------|-----------|-----------|
| | | Total No. | Total number decreased | Decreased to normal 2-10 mm. | Total No. | Converted |
| Mo. State San. | No. | 100 | 62 | 26 | 87 | 39 |
| | % | | 62 | 26 | | 45 |
| V. A. ⁴ | No. | 184 | 94 | | 190 | 82 |
| | % | | 51 | | | 43 |

TABLE IV
Exudative Disease

| | | Total No. | Improved marked or moderate | Marked improvement only | Minimal improvement or none |
|--------------------|-----|-----------|-----------------------------|-------------------------|-----------------------------|
| Mo. State San. | No. | 36 | 23 | 16 | 13 |
| | % | | 63.8 | 44.4 | 36.2 |
| V. A. ⁴ | No. | 222 | 189 | | 21 |
| | % | | 85 | | 10 |

TABLE V
Cavitation

| | | Total No. | Healed or lost to view | Became smaller | No change or larger |
|--------------------|-----|-----------|------------------------|----------------|---------------------|
| Mo. State San. | No. | 32 | 12 | 6 | 14 |
| | % | | 37.5 | 18.8 | 43.7 |
| V. A. ⁴ | No. | 182 | 47 | 67 | 68 |
| | % | | 26 | 37 | 37 |

completely, 1 improved, and 1 had no improvement. Canada reports that in 10 cases 8 had an increase of atelectasis.¹²

Laryngeal-bronchial tuberculosis: This type of complication is always serious because of the slow response to local treatment, end results of stenosis with all its complications and the poor prognosis in many cases. Several of the cases were terminal, while others, in spite of positive sputum and bronchial tuberculosis, had stable x-ray findings with no evidence of active lesions. In many of these cases exhaustive study, including laminagraphs, revealed no "feeder" focus; and when the bronchial granulations healed, the patient's sputum became negative and remained so. There were 31 cases of laryngeal or bronchial tuberculosis. Only those cases having positive sputum and bronchoscopic evidence of granulations or ulcers of the larynx, trachea or bronchi were chosen. Seventeen (54.8 per cent) cases healed, 6 (19.35 per cent) improved, 6 (19.35 per cent) had no improvement, and 2 (6.5 per cent) had converted sputum but showed persistent granulation tissue. Of the 17 healed cases 9 had converted sputums. A few of the healed cases had single or bilateral cavities. The number of days of treatment ranged from 98 to 272. Lesions healed from 1 to 6 months after initiation of treatment, the average being about 3 to 4 months. Two of the "no-improvement" cases had had laryngeal tuberculosis from 6 months to 1 year and were terminal. These cases respond poorly to streptomycin although one case of 3 months duration, terminal with ulceration and partial sloughing of the epiglottis, and having massively enlarged bilateral cervical glands and extensive granulation of the pharynx and larynx, healed in 3 months. Eleven cases of the 31 had converted sputums. One case improved enough for pneumonectomy and a postpneumonectomy case healed ulcerations of the bronchial stump. Streptomycin is of the utmost benefit to those patients needing resection, but are delayed because of bronchial tuberculosis.

Our results do not seem to compare favorably with those on higher dosages, but perhaps the severity of some of our cases and their chronicity was an unfair test of the 0.5 gram dosage.

Thoracic surgery: It is most difficult to evaluate the use of streptomycin used routinely in thoracoplasties and resections. Sixteen cases received streptomycin 1 week to 1 month before thoracoplasty and continued receiving the drug for 4 to 6 months. One was given streptomycin because of a bilateral spread of the disease after the first stage. The disease was promptly controlled and 2 more stages were carried out with resultant sputum conversion. Since none of the 15 cases had a spread of their tuberculosis during surgery, the use of streptomycin was probably unnecessary. Prevention of a spread cannot be credited to strep-

tomyacin since epidural anesthesia used routinely here results in almost no cause of spreads during thoracic surgery.¹³

Of the 6 cases of pulmonary resection receiving streptomycin 1 to 3 months before surgery, each had tuberculosis with bronchiectasis for which resection was carried out. All patients were negative following surgery and none had spreads.

Five cases which we were packing daily with plain gauze had widely incised subcapular infections. Routine smears of the infection were negative for tuberculosis bacilli; nevertheless we feel the infections were definitely tuberculous. All cases except 1 healed, and all patients were of the opinion that there was a marked decrease in the amount of drainage and in their symptoms. One case with a pleural-cutaneous fistula did not heal, but this patient had had a draining subcapular infection for several years before sanatorium admission.

Anal Fistula: Three cases having positive sputum had rectal or anal fistuli, which healed completely while taking streptomycin. One case was twice operated previous to streptomycin, but the internal fistulous opening could not be found. Curettements of the tract revealed tuberculous tissue. Drainage ceased in all cases in three days following initiation of streptomycin even though one case had had a fistula for 20 years.

Draining Cervical Sinuses: Three cases with cervical sinuses were treated with streptomycin. All gave a history of drainage for over 1 year, and all healed during the course of the drug. One had recurrence after streptomycin was stopped. This patient, however, had extensive skin destruction of the upper one fourth of the anterior part of the chest which healed about 1 month after streptomycin was started.

Bone: Five cases were treated for tuberculous osteomyelitis. Two had Pott's disease; 1 had tuberculous destruction of the knee joint with massive skin destruction, swelling and draining sinuses; and 2 had tuberculous osteomyelitis of the sternum. An interesting case was that of an 8 year old negro girl with symptoms and roentgenographic evidence of tuberculosis of the bones of both wrists, finger and a pericarditis with effusion. This patient actually receiving more than 0.5 gram in proportion to her size and age, had complete cessation of all symptoms in 3 months with roentgenographic evidence of healing of all bone lesions and disappearance of the pericarditis. One of the cases of Pott's disease had a surgical fusion at the time streptomycin was started and healed nicely. The other had had a fusion 4 years previously, but subsequently developed a large abscess in the right lumbar region with a fistulous tract extending upward and crossing the lower dorsal vertebrae to the bronchi of the medial basal segment of

the left lower lobe from where she constantly coughed and raised the pus. After incision of the abscess, she was given streptomycin intramuscularly and irrigations of the fistulous tract. All lesions healed and she became symptom free. The patient with the draining knee had skin grafting of the area of destruction with 100 per cent "take" of the graft even though the sinuses were still draining. The sinuses subsequently healed; fusion of the knee took place; and the patient is symptom free 9 months after discontinuance of streptomycin.

Genito-Urinary: Eight cases were treated for tuberculosis of the genito-urinary tract. Three cases had tuberculous epididymi which were either draining at the time or were surgically removed with spillage of infected material into the wound. All healed by primary intention with the sinuses healing in 1 month and remaining healed. One case had a nephrectomy with primary wound healing. Five cases had positive urine with severe cystitis diagnosed by cystoscopy. Although streptomycin gave marked relief in 4 of the 5, none had converted urines. The case with no response had contraction of the bladder to 60 cc. capacity. Cystoscopy in these cases revealed almost total healing of the severe cystitis. The reports of others are also discouraging regarding cures with higher dosages of streptomycin in tuberculosis of the kidney.^{4,5,10}

Intestinal: Seven had severe symptoms of intestinal tuberculosis, one of which was diagnosed by barium enema. All had symptomatic relief in 3 days to 1 month, with only one case having recurrence of symptoms after discontinuance of streptomycin.

Bronchiectasis: Five positive sputum cases were treated for bronchiectasis diagnosed by bronchography. All had fibrotic disease. Basing our treatment on the probability of tuberculosis of the terminal bronchi, we found only 2 cases had conversion of sputum and none showed more than a minimal improvement in their x-ray films.

Miscellaneous: One case with evidence of hematogenous spread of tuberculosis had tuberculous peritonitis diagnosed by laparotomy, lesions of the skin of the foot and finger and a subcutaneous abscess of the chest. All areas were proven tuberculous by guinea pig inoculation. In spite of the fact that the patient's x-ray film was negative, his sputum was positive by guinea pig inoculation. Nevertheless he responded excellently to streptomycin with complete alleviation of all symptoms and conversion of the sputum tested by the above mentioned method.

Toxicity, sensitivity, blood levels: There was not a single case of toxicity in our series. Only 2 cases had evidence of sensitivity by developing a rash which disappeared in a few days during streptomycin treatment.

Unfortunately our laboratory was not equipped to carry out sensitivity tests and blood levels at the initiation of our studies. We are now carrying out a limited number of sensitivity tests and find that the bacteria are sensitive to 0.05 to 0.2 micrograms of streptomycin before treatment. Keefer, et al.,⁴ report in their summary that 0.5 gram of streptomycin given intramuscularly results in blood levels of from 9 to 10 micrograms per cc. It seems reasonable, therefore, to assume that 0.5 gram dosage of streptomycin will have a bacteriostatic effect on the bacteria until resistance develops. There is a need for study to determine whether 0.5 gram daily dosages of streptomycin decreases or increases the period of formation of resistance of the tuberculous bacillus.

Discussion

From the results of our studies it appears that there is need for further investigation with lower dosages of streptomycin given at longer intervals than has been the practice in the past. There is evidence that constant high blood levels of streptomycin are not required to counteract the tubercule bacillus as is the case with penicillin and gram positive organisms. Although the cases of extrapulmonary tuberculosis reported in this series are not numerous enough for statistical significance, the author believes from his experience with cases now being treated at the Missouri State Sanatorium that 0.5 gram daily dosage of streptomycin with injections of 0.25 gram at 12 hour intervals is adequate for good response in tuberculous cavities, enteritis, anal and cervical fistuli, draining sinuses, tuberculous epididymi, and sputum conversion. Tuberculous abscesses can now be incised and drained without the fear that the resultant sinuses will seldom heal. Exudative disease and laryngeal bronchial tuberculosis, if of recent origin and not too extensive, respond satisfactorily to our dosage schedule. If more extensive and of longer duration, a higher dosage (1 to 1.5 grams) should be used. Urinary tract tuberculosis appears to respond to 0.5 gram dosage as well as to the higher dosage since neither seems to cure permanently the disease.

Streptomycin has immeasurably improved the prognosis in negro patients who usually present the exudative type of disease. The often fatal spread following thoracic surgery can now be combated with marked encouragement. The condition of patients needing thoracic surgery, but whose lungs or bronchi are so severely involved by tuberculosis that surgery is contraindicated, can usually be improved enough that surgical collapse measures or resections can be carried out.

However, streptomycin should not be used as a substitute for proper collapse measures, nor should these measures be delayed too long with the hope that they will be unnecessary. In many instances the optimum time is lost while waiting for the end results of streptomycin treatment. Since 0.5 gram daily dosage of streptomycin appears to give no toxic effects; and since the toxic effects on the vestibular apparatus and auditory nerve are the most serious concern of those using high dosages, our studies are of particular value. Furthermore, I believe it worthy to investigate the development of resistance of the tubercle bacillus to streptomycin given in this lower daily dosage (0.5 gram) with injections of 0.25 gram at 12 hour intervals.

SUMMARY

Total number of cases: 120 pulmonary and extrapulmonary tuberculosis.

Dosage: 0.25 gram at 12 hour intervals.

Temperature (64 cases): 67.2 per cent returned to normal; 12.4 per cent decreased to 99° F.

Weight (99 cases): 70.7 per cent gained weight.

Sedimentation rate of the red blood cells (100 cases): 62 per cent had a decrease.

Converted sputums (87 cases): 45 per cent converted.

Exudative lesions (36 cases): 63.8 per cent showed marked to moderate improvement roentgenographically.

Cavitation (32 cases): 37.5 per cent were healed or lost to view; 18.8 per cent became smaller.

Laryngeal-bronchial tuberculosis (31 cases): 54.8 per cent were healed; 19.3 per cent improved.

Toxicity: Not a single case was encountered in our series.

Although there was not a sufficient number of the extrapulmonary and thoracic surgery cases for statistical significance, evidence is accumulating that good response occurs in draining sinuses of the rectum, anus, cervical and epididymi; spreads from thoracic surgery; osteomyelitis; and symptomatic relief in urinary tract tuberculosis.

RESUMEN

Número total de casos: 120 casos de tuberculosis pulmonar y extrapulmonar.

Dosis: 0.25 gramo a intervalos de 12 horas.

Temperatura (64 casos): 67.2 por ciento volvieron a lo normal; 12.4 por ciento bajaron a 99° F.

Peso (99 casos): el 70.7 por ciento ganaron en peso.

Indice de sedimentación de los eritrocitos (100 casos): disminuyó en el 62 por ciento.

Espustos convertidos (87 casos): se convirtió en el 45 por ciento.

Lesiones exudativas (36 casos): el 63.8 por ciento demostró decidida o moderada mejoría en la roentgenografía.

Cavernas (32 casos): el 37.5 por ciento se cicatrizaron o se perdieron de vista; el 18.8 por ciento disminuyeron de tamaño.

Tuberculosis laríngeo-bronquial (31 casos): el 54.8 por ciento se curaron; el 19.3 por ciento mejoraron.

Toxicidad: No se encontró ningún caso en nuestra serie.

Aunque no hubo un número suficiente de casos extrapulmonares o de cirugía torácica para que tuvieran significado estadístico, se están acumulando pruebas de que ocurre una buena respuesta en fistulas con desagüe del recto, ano, ganglios cervicales y epidídimo; propagaciones consecutivas a cirugía torácica; osteomielitis; y alivio sintomático en tuberculosis del aparato urinario.

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Streptomycin in Tuberculosis of the Larynx*

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Most of the previously reported work on streptomycin therapy has utilized doses of the drug varying from one to three grams a day. The group of laryngeal cases reported here has been on doses far lower than the therapeutic doses generally accepted today. Streptomycin in doses of one to three grams a day produces a high incidence of toxic reactions, and this study of clinical material was undertaken with the express purpose of determining whether or not streptomycin in small doses, would prove to be of therapeutic value. The latest recommendations of the American Trudeau Society and the Veterans Administration are for a daily dose of streptomycin of about one gram for most cases of pulmonary tuberculosis and its extrapulmonary complications. In our series of cases we used both smaller doses and intermittent therapy, namely, 0.1 gram daily, 0.2 gram daily, 0.5 gram daily and 1 gram of streptomycin once weekly.

Tuberculosis of the larynx was chosen for this study because it offers a fairly accessible organ for direct and frequent observation. The same observer recorded findings in all of these cases, and only severe or moderately severe cases were chosen for treatment in order to provide sufficient gross pathologic findings to enable the observer to appreciate changes in the appearance of the larynx over a brief period. Laryngeal lesions have previously been reported as highly susceptible to improvement by streptomycin in the usual 1-2 gram daily dose, from 75-90 per cent of the cases.

Twenty-six cases were treated and observed over a period of three months. All twenty-six cases had far advanced pulmonary tuberculosis as well as laryngeal involvement and all had recent positive sputa for the tubercle bacillus. Five cases were given only 0.1 gram daily, 8 received 0.2 gram daily, 5 received 0.5 gram daily and 8 received 1.0 gram once a week. Each dose was administered intramuscularly, in a single injection daily or weekly over a period of three months.

The 5 cases receiving 0.1 gram daily were considered controls, as originally little therapeutic effect was expected and because the total of cases would have been appreciably reduced by following

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non-treatment controls. One showed slight improvement, three showed no improvement, and one case was much worse. One of the cases which did not improve required a tracheotomy because of a fixation of the vocal cords in the mid-line. Two of these five cases had previously been treated with large doses of streptomycin for tuberculous laryngitis and had been reported as healed, but the tuberculosis of the larynx recurred and they were included in this group.

The eight cases given 0.2 gram of streptomycin daily presented an entirely different picture. One showed no change; one improved slightly; one improved moderately, and the remaining five cases improved very markedly. These cases could not be considered healed, by mirror examination, but after three months of 0.2 gram of streptomycin a day, all had changed from moderately severe and severe cases of tuberculous laryngitis to mild or inactive cases. Two of the cases who had severe dysphagia, or pain on swallowing, were completely free of pain after 5 to 10 days respectively. One patient had a severe tuberculous laryngitis with obstructive symptoms, but after three months had a normal airway and her general improvement was marked by a weight increase of 35 pounds. The only case which showed no improvement was one which had previously improved under streptomycin therapy for tuberculous laryngitis and which had recurred.

Four of the five cases given 0.5 gram daily improved and one showed no improvement. Of the four improvements, one was slight, one moderate and two marked. Two cases with pain on swallowing cleared completely in 5 days to 2 weeks.

The last group of 8 cases received 1.0 gram of streptomycin only once a week. After three months, 6 of the 8 presented improvement, one mild, one moderate and four cases of very marked improvement. One case, presenting dysphagia, lost all symptoms of pain on swallowing after the second weekly dose.

On analyzing this series of 26 cases we find that percentage of improvement with small doses, 0.2 gram daily, 75 per cent; 0.5 gram daily, 80 per cent; and 1 gram weekly, 62 per cent, compares very favorable with the percentages of cases improving on 1-2 grams daily, i.e., about 70 per cent in all cases. This high percentage of improvement in laryngeal tuberculosis on doses of 0.2 gram daily, 75 per cent, as compared to no improvement under a course of 0.1 gram daily, implies a much lower limit of therapeutic effect than is ordinarily accepted and could be studied further. The cost of the drug is reduced considerably and the annoyance to the patient of several daily injections is lessened.

Five cases presented pain on swallowing. All five improved considerably in a short time and obviated the necessity of procedures

such as electrocautery, superior laryngeal nerve block or section and the use of anesthetic sprays. This one feature of streptomycin therapy in tuberculosis of the larynx has been universally noted.

Reports of a high percentage of cures with streptomycin in tuberculosis of the larynx may be misleading, however, if no mention is made of the condition of the larynx at a later date, after the cessation of streptomycin therapy. Several of the cases reported in this series had previously been reported as streptomycin cures, but the laryngitis recurred. In the series of 26 cases reported here, especially in the cases noted as clinically improved at the cessation of 3 months of therapy, several recurrences have already been observed, and continued observation of the remaining cases will doubtlessly uncover more. The improvement is temporary in many cases. Permanent cure depends on arrest of the pulmonary process.

The main toxic effect of streptomycin has been on the vestibular apparatus. Deafness is rare, but vestibular dysfunction occurs in the majority of the cases treated with 2 grams daily, and less frequently with 1 gram daily. In this series there were no complaints of deafness, and only one individual complained of dizziness, but the caloric responses here were normal. Toxicity to smaller doses, 0.5 gram and less, as used here, is apparently insignificant.

As for resistance of the tubercle bacillus to the streptomycin, it is conceivable that smaller doses will have the same end-result as larger doses. These 26 cases were examined for evidence of resistance at the onset of treatment, but the presence or absence of resistance at the conclusion of the therapy has not been determined as yet, for most of the cases recently completed the therapy. Four of the twenty-six cases had previous streptomycin therapy for tuberculous laryngitis. None of these showed any appreciable improvement in this series and studies of the tubercle bacilli showed that a resistance had developed after the first or during the second course of therapy. The twenty-two cases without previous streptomycin therapy had susceptible or sensitive bacilli. However, at the conclusion of the therapy of 0.2 and 0.5 gram daily, we have already shown a well marked resistance in five cases, and the laboratory work on the other cases has not been completed as yet.

CONCLUSIONS

- 1) Small and intermittent doses of streptomycin down to 0.2 gram daily, will give the same clinical improvement in cases of laryngeal tuberculosis as larger doses, and will especially relieve the severe pain as in the larger doses.

2) A large percentage of recurrences of the disease may occur no matter what dose is used originally.

3) Toxicity is negligible with the smaller and intermittent doses, but the tubercle bacilli develop a resistance to small doses just as they do toward larger doses of streptomycin.

CONCLUSIONES

1) Las dosis pequeñas e intermitentes de estreptomicina, hasta de 0.2 gramo al día, da la misma mejoría clínica en casos de tuberculosis laríngea que las dosis más grandes y especialmente alivia el dolor severo lo mismo que las dosis más grandes.

2) Puede ocurrir un alto porcentaje de recidivas de la enfermedad, no importa cual sea la dosis empleada al principio.

3) La toxicidad con las dosis pequeñas e intermitentes es insignificante, pero el bacilo tuberculoso desarrolla resistencia a las dosis pequeñas en la misma manera en que la desarrolla con las dosis más grandes de estreptomicina.

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Aerosol Antibiotic Therapy in Suppurative Diseases of the Lung and Bronchi*

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Inhalation therapy has become very popular both with physicians and the laity. While the use of antibiotics by nebulization is rather recent, the utilization of germicidal mists and therapeutic gases dates back many years. Those interested in a complete review of the historical background for aerosol therapy should read Segal's excellent article on the subject.¹

The original report on penicillin aerosolization was made by Bryson and his associates² in 1944 and was an outgrowth of their work on the physical and biologic properties of aerosol for the Technical Division, office of the Chief, Chemical Warfare Service. Since then, stimulated by their findings, clinicians have made exhaustive trials with this method in pulmonary infection not only with penicillin but also with the sulfonamides, the sulfones and more recently with streptomycin.

While this report is limited to the results obtained in suppurative diseases of the lungs and bronchi by penicillin and streptomycin aerosolization, it should be noted that infectious asthma, pneumonia, laryngotracheobronchitis and pulmonary emphysema associated with infectious bronchitis or bronchiectasis were also thus treated. However, as is the case with reports of others, the number of patients in the latter group is too small to warrant final evaluation.

When one realizes the extensiveness of the inner surface of the lungs there is little wonder that effects similar to that of intravenous injection can be obtained by inhalation. In fact both Bryson³ and Barach^{4,5} and their associates have demonstrated in the experimental animal and in humans that a more uniform blood level of penicillin can be maintained by the inhalation method than by intermittent intravenous or intramuscular injections. Levine⁶ has gone even further and has satisfied himself that aerosol penicillin will effect improvement in bronchiectasis when other methods fail.

That aerosolized materials when inhaled penetrate the outer-

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most air sacs of the lungs and are uniformly distributed was demonstrated by Krueger, et al,⁷ using India ink and radioactive chromic phosphate as indicators. High local or topical concentrations are thus made possible.

The detection of penicillin in the blood and urine after administration of penicillin aerosol is proof of its absorption. However, it does not follow that the blood level necessarily is a measure of its topical effectiveness. It has been shown that satisfactory clinical results can be obtained with low and even no penicillin levels. It is for this reason that Segal⁸ and his associates feel that the determination of blood levels is more of academic interest than of practical value. The clinical course is a better criterion of the local effectiveness of penicillin aerosol. Besides, factors other than alveolar absorption determine blood levels. These as listed by Segal⁹ are the equipment used, the dosage and types of penicillin given, the absorption variations of accumulated pus and secretion and the technic of determining blood levels.

More recently Bryson¹⁰ has shown that the bacteriostatic effect of penicillin and streptomycin aerosol can be enhanced by using



FIGURE 1: Method of Aerosolization,

a detergent as the solvent for the drugs. Detergents or wetting agents have the properties of emulsification and of reducing surface tension. These properties serve to break up pus and cellular detritus and in this manner assure better contact between micro-organisms and the antibiotic. Already the combination of penicillin with detergent solutions has resulted in reduction of mortality in mice with experimental pulmonary disease as compared with a control series treated with penicillin aerosol alone. Clinical trials are being made and while a final report cannot be given at this time, results indicate that wetting agents likely will play an important role as adjuncts to simple aerosol therapy.

Intrabronchial instillation of penicillin or streptomycin has proved of additional value in some instances in which aerosol therapy was used and according to Siltzbach¹¹ better results than with aerosolization can generally be obtained. The method involves inconvenience to the patient and in my experience is seldom necessary. Furthermore, the use of this method does not obviate the interference offered by pus for contact of the drug with the micro-organisms. I believe that wider use of detergents will increase the efficacy of aerosol therapy without necessitating bronchoscopic or tube intubation instillation of antibiotics.

It has been long recognized that a knowledge of the bacterial content in suppurative pulmonary disease is not of real importance.



FIGURE 2: Microscopic section of a dilated bronchus of an excised lobe untreated prior to operation. Note pus and cellular debris within bronchial lumen.

The introduction of penicillin and particularly streptomycin has changed the picture since it is considered essential to know whether one is dealing with sensitive or resistant organisms. This information is especially valuable if the benefits of multiple antibiotic



FIGURE 3: Microscopic section of a dilated bronchus of an excised lobe treated with penicillin aerosol prior to surgery. Note clear bronchial lumen.

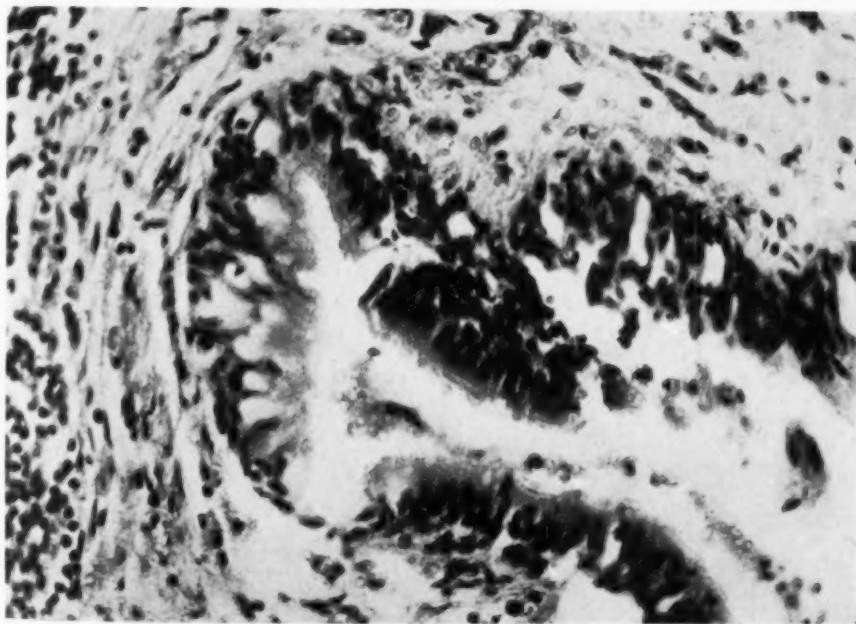


FIGURE 4: Same as figure three—high power view.

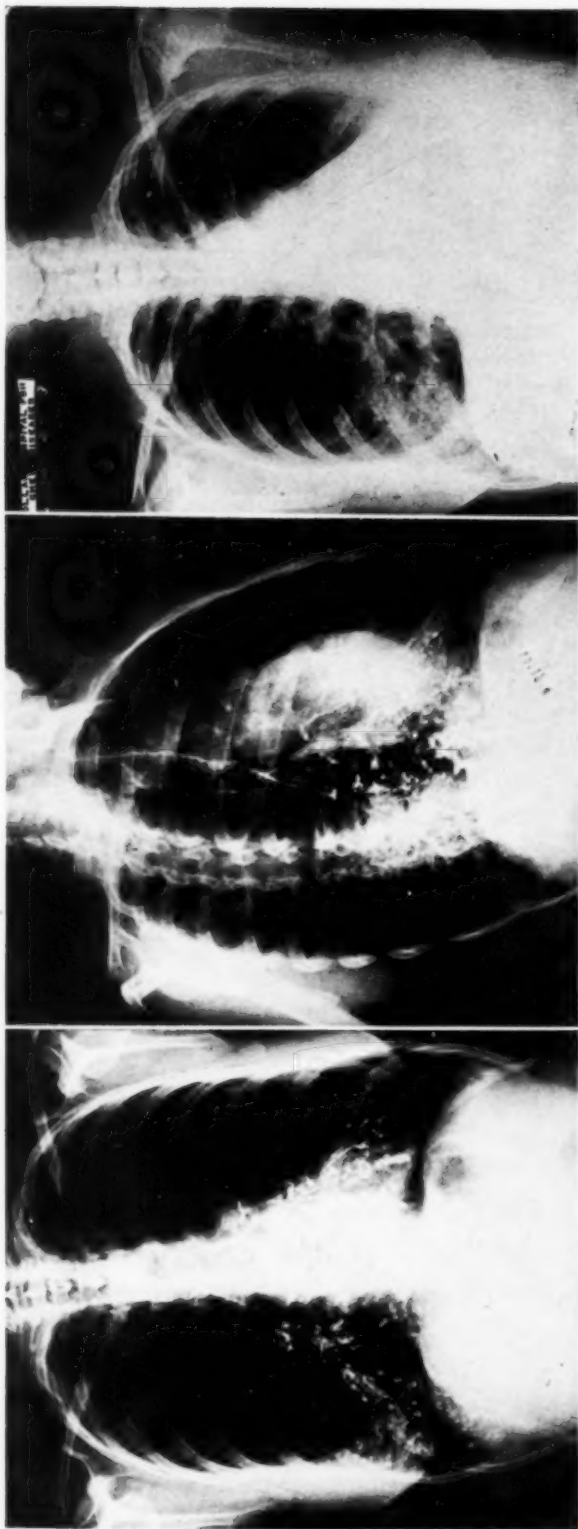


FIGURE 5

FIGURE 6

FIGURE 7

Figure 5: White female, aged 32 years, admitted with cough and expectoration of foul sputum. Symptoms of 13 years duration. After 3 weeks of penicillin aerosol cough and sputum ceased. Bronchogram shows saccular bronchiectasis of the left lower lobe.—Figure 6: Same patient, oblique projection showing saccular dilatations.—Figure 7: Same patient after left lower lobe lobectomy. Residual lipiodol shadows are seen in the right lower lobe. Symptom free.

therapy is sought. Yet, despite what has just been said, I feel that aerosol therapy can be properly carried out without facilities for such determinations. It is nice to have them but from a practical point of view the clinical course is a good therapeutic guide. Our own and the experience of others indicate that the vast majority of patients who respond favorably to antibiotic aerosol therapy do so to penicillin alone.

The response to aerosol therapy is rapid and decisive; in fact in some instances it is dramatic. Fever and toxicity subside, the amount of daily sputum is diminished and in many cases secretions are entirely abolished, if the character of the sputum is foul, the odor is lost, serial roentgenograms of the chest reveal partial to complete resorption of the perifocal infiltrates and gross and microscopic sections of excised lungs show dilated but clean bronchi in contrast to bronchi filled with cellular debris and pus in untreated lungs or in cases which fail to respond to treatment. Those who have followed their cases with bacteriological studies have been impressed with the disappearance of susceptible micro-organisms.

If the above effects of antibiotics were permanent, the management of respiratory disease would indeed be simple. Unfortunately, this is not the case. In suppurative bronchiectasis the best results are obtained in the surgical cases in which penicillin and/or streptomycin aerosol seems to improve the surgical risk for the patient. He comes to the operating table either symptom-free or with minimal cough and expectoration. It is a general observation that thus prepared the patient is anesthetized with little or no difficulty and maintains the anesthetic state for many hours without ill effects and postoperative complications such as pneumonia and atelectasis are minimized.

In the non-surgical cases, the effects of penicillin and streptomycin are temporary and in most instances recurrences take place. But even these patients may sustain their attained improvement for months or longer and if symptoms do return, may again benefit by re-institution of aerosol therapy. In some, supplementary deep x-ray therapy may give more permanent results.

Prior to the introduction of the antibiotics, early incision and drainage was considered urgent in the proper management of acute lung abscess. Amelioration of symptoms such as fever, toxicity, cough and expectoration and obliteration of the abscess cavity followed in only about 15 per cent without surgical intervention. The use of penicillin singly or in combination with streptomycin has reversed the picture in so far as symptomatic relief is concerned. The follow up of "cured" cases has not been sufficiently long to determine whether spontaneous obliteration of

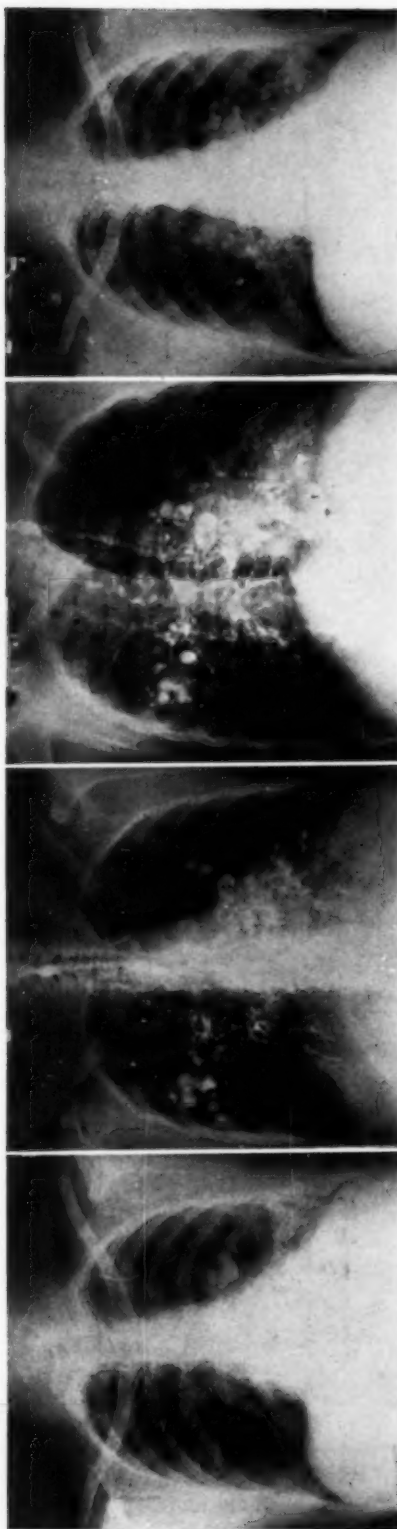


FIGURE 8

FIGURE 9

FIGURE 10

FIGURE 11

Figure 8: White male, aged 43 years, admitted with cough, expectoration of purulent sputum, and history of repeated hemoptyses. Roentgenogram shows broncho-pneumonia left lower half of lung field and multiple ring shadows in right mid lung region. Duration of symptoms since childhood.—*Figure 9:* Same patient after one month of penicillin aerosol. Occasional cough not productive of sputum. Bronchogram shows cystic bronchiectasis of both lungs.—*Figure 10:* Same patient, oblique view.—*Figure 11:* Same patient. Roentgenogram shows residual lipiodol shadows. Note almost complete resolution of pneumonia in left lung. Symptom free for past ten months.

abscess cavities has been materially increased above the figure given.

One thing is clear, surgery is no longer an immediate issue and when it does become necessary the patient is usually a much better candidate than was the case prior to antibiotic therapy. Moreover, the tendency now is to favor excision of the involved segment of the lung rather than pneumonostomy as it is believed that in many cases dilatation of the radicles of the bronchus draining the abscess cavity exists either at the time the lesion is discovered or develops later. As in bronchiectasis so in lung abscess, the preoperative preparation of the patient can be made more ideal and postoperative complications minimized by aerosol therapy.

Toxic effects such as sore tongue or stomatitis, edema of the lips or mucosa of the mouth, generalized urticaria and dyspnea have been reported. In the series of cases herein presented, sore tongue was encountered twice and dyspnea in two other instances; the latter in the group comprising infectious asthma and fibrosis with emphysema. Stomatitis is readily controlled by proper oral and dental hygiene and rinsing of the mouth with warm saline solution at the completion of each treatment. The allergic reactions mentioned above are easily managed by any of the anti-histamine drugs. If dyspnea develops, discontinuing the drug brings about early relief. Subsequent re-institution of inhalations may not bring about return of the complaint. In one case, however,

| LUNG ABSCESS | | |
|----------------------------------|--|---------|
| | Type of Surgery | Results |
| SURGICAL SIX CASES | PNEUMONOSTOMY 1 case | Well |
| | PNEUMOSTOMY + lobectomy 2 cases | Well |
| | LOBECTOMY 3 cases | Well |
| NON-SURGICAL | 2 patients improved and awaiting surgery. | |
| FOUR CASES | 2 patients obtained spontaneous closure of abscess cavity. In one, cavity has remained closed two years; in the other, recent recurrence has taken place after 6 months of closure. Latter patient awaiting surgery. | |

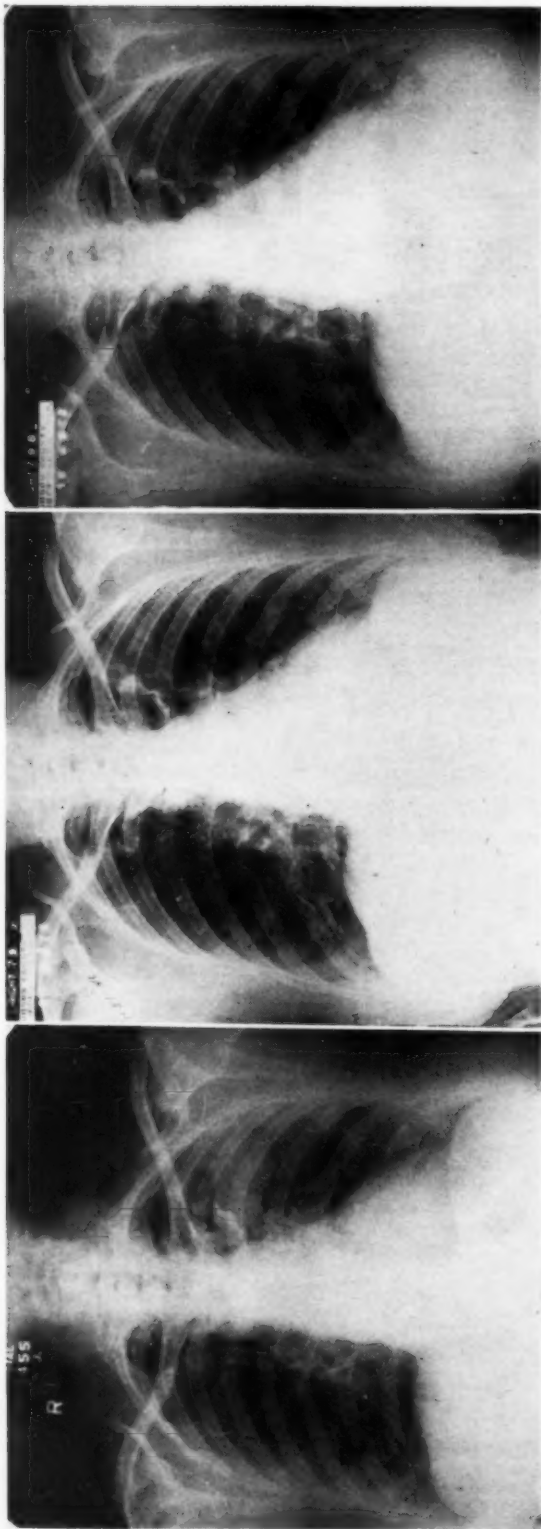


FIGURE 12

FIGURE 13

FIGURE 14

Figure 12: White diabetic female, aged 53 years. Admitted from another hospital with cough and expectoration of foul sputum. Despite parenteral penicillin and sulfa therapy for 2 months prior to admission, improvement failed to take place. Roentgenogram shows a large abscess cavity in the left upper lobe.—Figure 13: Same patient after 10 weeks of penicillin aerosol therapy. Note disappearance of cavity leaving residual infiltrate. Symptoms minimal at this time.—Figure 14: Same patient after four months of aerosol therapy. Note complete resolution of residual infiltrate shown in figure 13. Symptom free.

the aerosol therapy had to be discontinued permanently because dyspnea returned each time aerosolization was re-established.

Various methods of nebulization are in use. The fundamental principle is that the nebulizer be so constructed as to emit small particles, 5 microns in diameter or less, if penetration of the



FIGURE 15



FIGURE 16

Figure 15: Same patient. Bronchogram showing absence of bronchiectasis.—

Figure 16: Same patient 1 year after discharge. Note absence of any abnormal change in the left lung. Has been symptom free since discharge.

BRONCHIECTASIS

| | Pneumonectomy | Lobectomy | Lobectomy plus Lingulectomy |
|--|-----------------|------------------|--|
| SURGICAL | | | |
| 18 | 6 | 9* | 3 |
| CASES | | | |
| *One patient had right middle and lower lobes excised. | | | |
| | Symptoms Abated | Symptoms Reduced | Recurrences |
| NON-SURGICAL | | | |
| 18 | 3* | 15** | In 3 instances all derived from "Symptoms Reduced" group. In each instance severity and character of symptoms as existed prior to aerosol therapy, returned. Two have responded favorably to re-institution of previous therapy. |
| CASES | | | |

*Only 6 months Follow-up.

**Followed from 3 months to 2 years.

smallest bronchioles and the alveoli is to be expected. Larger particles are impinged by convection in the nose, throat and upper respiratory passages and are undesirable. Nebulization is generally accomplished by employing a stream of oxygen from a high pressure cylinder to a serviceable nebulizer. In the beginning of our work a Y tube was attached to the rubber connection between the regulator of the oxygen tank and the nebulizer. During inspiration the open end was closed by a finger which was released during expiration resulting in the escape of oxygen during this phase of respiration. More recently the Y tube has been replaced by a demand valve which saves the oxygen that used to be lost in the expiratory phase. To minimize the loss of the antibiotic during expiration a rebreathing bag is attached to the nebulizer. A flow of 6-10 liters per minute of oxygen may be employed. Either normal saline or distilled water is used as the diluent.

Patients too ill to cooperate with the demand valve arrangement described above, may be given penicillin or streptomycin either parenterally for several days when sufficient improvement takes place to switch to aerosol or through an oronasal meter mask by attaching the nebulizer to the latter. Patients with dyspnea and/or cyanosis who require oxygen in addition to aerosol therapy may be given both through a head tent. This method is particularly useful in children. Prigal¹²⁻¹⁴ described a combined steam generator and aerosolizer which produces a warm moist aerosol capable of giving high therapeutic blood levels of penicillin. He claims it is more economical to operate and the small size makes it convenient for use at home, in the office, or in the hospital.

The results in 36 cases of bronchiectasis and in 10 of lung abscess are tabulated below. No further explanatory remarks are necessary except to stress that the figures amply support the statements made above regarding the clinical and anatomical effects of aerosol therapy in bronchopulmonary suppuration. Finally, it is to be noted that in only three instances was penicillin supplemented by streptomycin.

Since the paper was submitted for publication, we have utilized a small bedside or table pump for nebulization instead of oxygen. Pumps by a number of manufacturers are now on the market at very reasonable cost. For patients who have obtained the initial improvement hand bulb nebulizers which produce a fine mist are now available for continued therapy at home.

SUMMARY

1) The results in 46 cases of bronchopulmonary suppuration treated by aerosolized antibiotics are reported.

2) Methods of nebulization are briefly reviewed.

3) It is stressed that the local concentration and the topical effectiveness of the antibiotics judged by the clinical and anatomical course of the disease are more important criteria than the blood level.

4) Penicillin and/or streptomycin aerosol therapy usually brings about appreciable clinical and anatomical improvement and therapy minimizes the operative risk in patients able to meet requirements for excisional surgery.

5) In non-operative cases of bronchiectasis attained improvement may be maintained for months or longer although recurrences are frequent. Favorable responses to aerosolization may be repeatedly obtained.

6) With the use of antibiotics surgical drainage is no longer an emergency in lung abscess. Because bronchiectasis not infrequently complicates lung abscess, extirpation of the involved lung segment is favored.

7) Whether the number of lung abscesses which heal spontaneously has increased cannot be stated unequivocally at this moment.

8) Antibiotics by nebulization are more convenient for the patient and their effectiveness equal, and in some instances more definite, than parenteral administration.

RESUMEN

1) Se informa sobre los resultados obtenidos en 46 casos de supuración broncopulmonar tratados con aerosoles de antibióticos.

2) Se repasan brevemente los métodos de nebulización.

3) Se recalca que la concentración local y la eficacia tópica de los antibióticos, a juzgar por la evolución clínica y anatómica de la enfermedad, son criterios más importantes que el nivel sanguíneo.

4) El tratamiento con aerosoles de penicilina o estreptomicina, o de ambas drogas, generalmente causa apreciable mejoría clínica y anatómica y reduce al mínimo el riesgo operatorio en pacientes que satisfacen los requisitos para la cirugía de excisión.

5) En casos de bronquiectasia que no pueden ser operados es posible mantener la mejoría obtenida por periodos de meses o más, aunque son frecuentes las recidivas. Pueden obtenerse repetidamente las respuestas favorables a la terapia con aerosoles.

6) Gracias al uso de antibióticos, la canalización quirúrgica ya no es una emergencia en el absceso pulmonar. Como quiera que con bastante frecuencia complica la bronquiectasia al absceso pulmonar, se favorece la extirpación del segmento pulmonar invadido.

7) Al presente no se puede declarar en forma inequívoca si ha

aumentado el número de abscesos pulmonares que se cicatrizan espontáneamente.

8) La administración de antibióticos nebulizados es de más conveniencia al paciente y su eficacia iguala, y en algunos casos supera, a la administración parenteral.

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Discussion

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Nebulization therapy is effective in providing at least temporary reduction of pulmonary secretion in most patients who have non-surgical bronchiectasis. Primary bronchial dilatation is not affected. The patients are still subject to the hazards of a deformed bronchial tree. It is strongly recommended that they continue therapy at home.

In asthma caused by susceptible micro-organisms, aerosol penicillin and/or streptomycin are indicated whether the chronic or

the acute active stage is encountered. Four daily sessions with antecedent use of one-fourth to one-half per cent neosyneprine and a solution containing 100,000 units of penicillin or/and 0.025 grams of streptomycin with eight liters of oxygen, and followed by one or two cc. of normal saline are used. The results are almost unbelievable; among our 23 cases of infectious asthma seen during the last 15 months 16 were completely relieved and three others were materially aided.

Krasno, L., Karp, M. and Rhoads, M. S. ("The Inhalation of Dust Penicillin," *Annals of Int. Med.*, 28:607-608, March 1948), have described a mask for home and office use. This mobilizes penicillin dust with a resultant marked diminution of bacterial flora, improvement in signs and symptoms, and an effective blood level. We are in the process of investigating this as an adjuvant therapy in tuberculosis, after the maximal benefit has been reached via parenteral administration.

Reactions to Penicillin in Aerosol

Several reactions have occurred: Two with mild generalized erythema... three with localized irritation about the mouth and tongue with soreness, dryness and some edema. One patient had sternal discomfort, which was abated with oral anti-histamines.

Penicillin or streptomycin or both via inhalation are not cures, but a valuable adjunct in treating bacterial conditions of the upper and lower respiratory tract.

Allergic reactions to penicillin may occur with any method of administration. No cases of vertigo, arthralgia or eighth nerve involvement occurred in our streptomycin treated cases by nebulization.

One should not depend completely on penicillin inhalations where complete control is not available, i.e., the aged, in the home, and where bacteremia may exist.

Mechanical obstructions in the respiratory tract, even with the use of detergents, reduce the efficaciousness of the method.

Recurrences following discontinuation of therapy in chronic non-surgical disease were common.

Until we have available a method of introducing effective antibiotic therapy in acute and chronic respiratory diseases, easily administered—without the high cost of oxygen, the tediousness of administration and close supervision—aerosols should be limited to hospital and office use, and only the occasional patient at home. One injection of procaine penicillin is much less trouble than a minimum of 80 minutes of supervised nebulization.

Bronchogenic Carcinoma*

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During the past eleven years from 1937 to 1948, 50 cases of primary lung tumor were observed at Muirdale Sanatorium. Three of these cases were bronchial adenoma; although they are considered as potentially malignant, they will not be included in this presentation. There remain 47 cases of primary bronchogenic carcinoma for consideration. The majority of these cases had been diagnosed as pulmonary tuberculosis prior to admission and a few were sent in for observation and diagnosis. Only two patients had both tuberculosis and bronchogenic carcinoma. Five of the 47 patients with bronchogenic carcinoma were treated for a number of months at home as cases of pulmonary tuberculosis. All entered Muirdale Sanatorium later with inoperable lesions although two had apparently operable lesions when first seen by their physicians.

That the two diseases may simulate one another is well known; but there are sufficient differential diagnostic points to enable one to make a diagnosis without too much difficulty or delay. In both diseases early diagnosis is stressed, because the prognosis is directly proportional to the stage of the disease. In far advanced tuberculosis, many patients can be saved, but in advanced bronchogenic carcinoma the prognosis is hopeless.

Of the 47 cases, 35 were proved: 17 by postmortem examination, 17 by biopsy, and one by the presence of tumor cells in the pleural fluid. The remaining twelve cases were diagnosed on the basis of clinical, roentgenologic and bronchoscopic findings. Four of these twelve cases had rib metastases, and one had paralysis of the right hemidiaphragm and vocal cord.

Incidence, Age, Sex and Race

There has been considerable discussion during the past thirty years as to whether the increase in primary bronchogenic carcinoma is apparent or actual. The matter is a controversial one. We merely wish to express the opinion that the reported increase

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is relative rather than absolute. We attribute the apparent increase to improved diagnostic methods, such as greater use of radiologic procedures, the bronchoscope and a better concept of the pathology of lung tumors. We are cognizant of the fact that with an increase in longevity, people have more of an opportunity to die from malignancy than in the younger age groups.

Primary bronchogenic carcinoma is now second only to carcinoma of the stomach as a cause of cancer death. At postmortem examination it is found in slightly over one per cent of all necropsies and comprises 10 per cent of all carcinoma found at postmortem examination.

Primary bronchogenic carcinoma may occur at any age, but there are suprisingly few cases reported under 40 years. Bjork¹ in an analysis of 345 cases from the Brompton Hospital for diseases of the chest in London, reports 87.8 per cent of the cases were 40 years and older. The average age of our patients was 55.4 years. Fourteen were between the ages of 40 to 50, twenty-two were between 50 and 60 years, and eleven were over 60 years. The youngest patient was 40, and the oldest was 73 years old.

Thirty-five of our patients were males and 12 were females, giving a ratio of three to one. In a larger series of cases reviewed by Bjork,¹ Ochsner and his associates,² and others, approximately 90 per cent were males. All of our cases were white, but according to Ochsner and his associates² the ratio between negro and white is two to one in favor of the white race.

Etiology

The cause of bronchogenic carcinoma is not known. There have been numerous reports suggesting chronic pulmonary irritation as an etiologic factor. As yet there has been no proved relationship between bronchogenic carcinoma and the numerous causes of chronic pulmonary irritation.³ Two patients were molders who had roentgenologic evidence of silicosis; one proved on necropsy to have both diseases. Three other cases had considerable foundry dust exposure with questionable silicosis, as indicated by the roentgenogram, but no postmortem examination was permitted in these cases.

Pathology

It is now generally agreed that bronchogenic carcinoma arises from an undifferentiated stem cell in the basal membrane of the bronchus. Grossly, the right lung is more frequently involved than the left lung. From roentgenologic and postmortem findings in our cases, the right lung was the site of the primary lesion in 23 cases and left lung in 18 cases. In the remaining six cases the

primary site could not be determined. Ochsner and his associates,⁴ in an analysis of 4732 cases collected from the literature, found that 58.3 per cent of the tumors were in the right lung and 41.7 per cent in the left lung. The upper lobes are more frequently involved than the lower lobes. The tumors are primarily hilar in location, arising in the majority of cases from the main stem bronchi or the secondary, lobar bronchi.

Microscopically bronchogenic carcinoma is classified into three types.* Squamous cell carcinoma is the most frequent. It offers the best prognosis as it grows slowly and metastasizes late. Undifferentiated cell type is slightly less frequent than the former, and adenocarcinoma, the third type, occurs in approximately 20 per cent of all the cases. Both the undifferentiated and adenocarcinoma are more rapid in their progress, metastasizing early with a correspondingly poor prognosis.

Bronchogenic carcinoma is noted for its widespread metastases. Ochsner and DeBakey,⁵ in an excellent article, review the incidence and site of metastasis in 3047 cases collected from the literature. The regional lymph nodes are most frequently involved, an incidence of 72.7 per cent. From a surgical standpoint the involvement of the regional lymph nodes is considered to be 100 per cent, and they are resected if possible. Of diagnostic importance are the supraclavicular, cervical, and axillary lymph node metastases, which occur in approximately 28 per cent of the cases. The next most frequent site of involvement is the liver, with the pleura, lung, bone, adrenal, kidney, brain and heart following in the order of their relative frequency.

In our series of cases the incidence of the various types of bronchogenic carcinoma in the proved cases is as follows: 14 were undifferentiated-cell type, 14 were squamous cell carcinoma and 4 were adenocarcinoma. Three of the adenocarcinomas occurred in women, and this corresponds to the usually reported high incidence of this tumor in that sex. One of our cases was unclassified histologically and in one other; in which the diagnosis was made by the presence of tumor cells in the pleural fluid, the cell type was not determined. We had one case of alveolar cell carcinoma. At the present time the histogenesis of this tumor is a matter of controversy. Some believe the tumor originates directly from the alveolar cells, but the majority of pathologists maintain that it arises from the basal layer of the bronchus in common with the other types of bronchogenic carcinoma.

*Acknowledgment: We wish to thank Dr. Joseph Kuzma, Director of Laboratories of the Milwaukee County Hospital, for assisting us in the pathologic classification.

Clinical Manifestation

Early recognition of primary bronchogenic carcinoma is of vital importance if effective cure is to be obtained, therefore a review of the clinical features is important. Only four of the 47 cases were considered as operable at the time of admission. These patients were discharged to their private physicians, and on follow-up it was discovered that none had surgery. Two patients are alive at the time of this writing; both are inoperable.

There are many reasons for the excessively high incidence of inoperability in these cases. One was the delay by the patient in seeking medical advice. An average period of 6.4 months elapsed from the time of the first symptom. The second factor was the delay in establishing the diagnosis after the patient had consulted a physician. This period was 4.3 months, giving the total duration of symptoms 10.7 months before diagnosis was made. The total duration of life from the onset of symptoms to death was only 14.5 months. Bjork¹ reports almost the opposite findings in analysis of 112 cases, the patient's delay was 3.4 months, and the physician's delay was 5 months, giving a total of 8.4 months delay before the correct diagnosis was established. These observations emphasize the necessity of the development of cancer consciousness both in the physician and the public.

The clinical picture of primary bronchogenic carcinoma is mainly respiratory in character. The symptoms are cough, expectoration, chest pain, hemoptysis, dyspnea and wheeze. Cough is the most common symptom and it occurred as the presenting manifestation in 31 of our 47 cases. Usually a number of these symptoms occurred at the same time, and it was impossible for the patient to establish a priority. Other first symptoms that brought patients to the physician were chest pain in seven, hemoptysis, loss of weight and dyspnea in two each, and loss of strength in one. When any of the above symptoms occur, singly, or in a group, in an individual 40 years of age or over, bronchogenic carcinoma must always be considered.

Weight loss was a very prominent symptom, the average loss being 24 pounds. While most of our patients continued to lose weight, some have maintained or even gained weight when on a sanatorium regimen. One of our patients gained 22 pounds over a 3 month period and then suddenly developed lymphangitic spread of his carcinoma, simulating miliary tuberculosis, with a rapid downhill course to death. The gain in weight and the presence of acid-fast bacilli in the sputum culture confused the diagnosis. Subsequently, the micro-organisms were found to be nonpathogenic.

Unfortunately, the presenting symptoms may be due to metas-

tases to other organs. The bones, (ribs and spine are the most common) brain, or distant superficial lymph nodes (cervical, supraclavicular and axillary) are frequent sites. Most patients had some elevation of temperature, and the degree of elevation depended upon an associated pneumonitis. When bronchial obstruction was present, there usually was a septic type of fever varying from 100 to 103 degrees F.

Blood counts were of no diagnostic significance, and a moderate anemia was present in only 12 cases, varying from three to four million RBC per cu. mm. Twelve other cases varied from 4 to 4.5 million RBC per cu. mm. In the remaining 23 cases the count was over 4.5 million. The hemoglobin value corresponded with the red blood cell count. Leucocytosis was present in the majority of cases; 10 were in the normal range and the rest had over 10,000 white blood cells per cu. mm. Twenty-three cases ranged from 16 to 26,000 WBC per cu. mm. The differential WBC revealed a slight shift to the left in 14 cases. Henkin⁶ reports a case in which the WBC rose to 85,000 and gradually dropped to 30,000 during a three month interval. Bone marrow puncture was not conclusive. However, bone metastasis was visible by roentgenogram five months after the height of the leukemoid reaction. He also states others^{6a,b} have reported similar leukemoid reactions in bronchogenic carcinoma.

The blood sedimentation rate was rapid in 12 of 14 cases in which it was determined. Two cases had a normal rate. Only two patients were tuberculin tested before admission, and both of these were positive. Of our 47 cases, 27 were tuberculin positive, 9 were negative and 11 were not tested after admission. Of the nine negative cases, five were negative to PPD₂, three to PPD₁ and one to 1-10 Old Tuberculin. One of the patients who did not react to PPD₂ was moribund, the other nonreactors were in good clinical condition. Obviously these negative reactors should never have been admitted to the sanatorium. This emphasizes the need and importance of tuberculin testing adults before making a diagnosis of pulmonary tuberculosis.

Pleural effusion was noted in 13 patients while under our observation and one had a bilateral effusion. Hemorrhagic pleural fluid is by no means always present. Ten of the effusions were aspirated, and clear or slightly cloudy fluid was obtained in eight, grossly hemorrhagic fluid in two. The differential cell count of the pleural fluid is not significant. In six cases the cell count revealed a lymphocyte count of 90, 83, 70, 35, 18, and 13 per cent. The first three counts would suggest a tuberculous effusion. One count revealed 60 per cent eosinophils, a very unusual finding. Tumor cells were present in six of the 10 cases examined. The

presence of tumor cells signifies metastasis to the pleura, and it is considered a contraindication to surgery. Not all pleural fluids contain tumor cells, small collections of fluid may be present along with atelectasis. This in itself would not constitute a contraindication to surgery. In our series, nine supraclavicular and cervical lymph nodes were positive on biopsy, and one inguinal lymph node was negative.

Seven of the 47 patients were sent to Muirdale Sanatorium because of positive sputum. Four of these cases had postmortem examination, and in only two could tuberculosis be demonstrated grossly and microscopically. In the three other instances we could not duplicate the positive results although numerous sputums and gastric aspirations were negative for acid fast bacilli.⁷ In view of our negative results we ignored the outside findings and considered them as inaccurate.

Diagnosis

Physical examination has marked limitations. Frequently no abnormal findings are noted. The latter depend upon the volume and location of the tumor tissue and upon the degree of bronchial obstruction with an associated atelectasis, bronchiectasis and pneumonitis. The presence of localized rhonchi, which may be associated with a respiratory thrill, may be the only indication of a partial bronchial occlusion. Clubbing of the fingers was noted in 10 of the 47 cases. This has no significance in itself, and merely indicated pulmonary diseases. However, the widely held belief that clubbing rarely or never occurs in bronchogenic carcinoma is erroneous.

A roentgenogram of the chest is paramount, and the examination of any patient is incomplete without one. The radiological manifestations will, of course, depend upon the stage of the disease. Early, there may be no abnormality, but, unfortunately, these cases are rarely seen. It may be necessary to employ various positions and techniques, including tomography,^{8,9} to visualize the lesion properly. In one of our cases, the latter procedure revealed a rib metastasis, otherwise obscured by a dense tumor mass. Bronchography is occasionally useful, and is of particular value in early, upper lobe and peripheral lesions. A perihilar mass is the most characteristic manifestation. There may be evidence of atelectasis, pneumonitis or emphysema. A single peripheral nodule may occur but this is relatively infrequent. Atelectasis was present in 25 of our 47 cases, obstructive emphysema was observed only twice. In a rapidly growing tumor central necrosis may occur and a cavity may be found. This was present in three of our cases.

Bronchogenic carcinoma may simulate any pulmonary lesion and should always be considered as a diagnostic possibility.

Bronchoscopy is also paramount. It not only affords an opportunity for a biopsy but also gives the surgeon information as to the state of the carina and trachea. If they are invaded, the primary tumor is not resectable. A positive bronchoscopic biopsy will be obtained in about 50 per cent of the cases. Meade¹⁰ in a report to the American Trudeau Society, states that there was about a 45 per cent positive bronchoscopic biopsy out of a total of 518 cases collected from three different authors. Thirty-four of our 47 cases had a total of 43 bronchoscopies. Twenty-two had biopsies and of these 16 were positive for carcinoma. In ten cases there was sufficient bronchoscopic evidence to indicate bronchogenic carcinoma. Eight patients had negative bronchoscopic examinations; however, negative bronchoscopic findings do not necessarily mean the absence of malignancy. Upper lobe lesions are difficult to visualize and peripheral lesions are practically never seen.

Tremendous advance has been made in the past few years in the cytological examination of bronchial secretions and sputum for tumor cells. The reports are very gratifying and various examiners¹¹⁻¹³ report positive findings varying from 80 to 90 per cent. According to Clerf,¹² cytological examination has conclusively demonstrated that carcinoma can be diagnosed in an additional 20 to 25 per cent of the cases whose lesions are beyond bronchoscopic vision.

An exploratory thoracotomy is a diagnostic procedure and should be resorted to in the presence of radiological evidence of a persistent or progressive pulmonary lesion in which all other diagnostic procedures have been negative, and in which all other causes of the lesion have been ruled out. There should not be too much delay in this decision, because metastasis may occur at any time.

We are in agreement with Jones¹⁴ and others^{15,16,2} that needle biopsy as a diagnostic procedure is a dangerous procedure and should not be used.

The treatment for bronchogenic carcinoma is surgical. Total pneumonectomy with resection of the bronchial and mediastinal lymph nodes is the usual procedure. Contraindications to surgery are paralysis of the diaphragm or vocal cords, metastasis, pleural effusion with the presence of tumor cells, involvement of the carina or trachea and very poor general condition of the patient. Some surgeons² do not necessarily consider paralysis of the diaphragm or vocal cords as a contraindication to surgery. Age is no contraindication. The incidence of resectibility at the time

of diagnosis varies; according to Ochsner and his associates² it is one out of three patients, and according to Lambert,¹⁷ one out of five. Only 4 of our 47 cases were considered operable; however, as previously stated, none of these had surgery. The operative mortality as reported in the literature varies from 20 to less than 4 per cent.¹⁴ In a series of 412 cases Ochsner and his associates report a five year survival rate of 8 per cent.

It is generally recognized that roentgenray therapy is only palliative, and is used for the relief of intractable pain or secondary pulmonary infection.

*Dr. J. D. Steele of the Surgical Department of Muirdale Sanatorium performed all the bronchoscopies.

SUMMARY

In an eleven year period at Muirdale Sanatorium, 47 cases of primary bronchogenic carcinoma were observed. These patients were sent in as cases of pulmonary tuberculosis. Thirty-five of the 47 cases were proved by postmortem examination, biopsy and one by the presence of tumor cells in the pleural fluid. Twelve cases were diagnosed on the basis of clinical, roentgenologic and bronchoscopic findings.

Two cases had both pulmonary tuberculosis and primary bronchogenic carcinoma.

The average age of our patients was 55.4 years. Our youngest patient was 40 years old and the oldest was 73 years of age. The ratio of male to female was 3 to 1.

Of the proved cases, 14 were squamous cell type, 14 undifferentiated-cell carcinoma, 3 adenocarcinoma and one alveolar cell carcinoma. Two cases could not be classified histologically.

The importance of early recognition of primary bronchogenic carcinoma is emphasized by the fact that only four of the 47 patients were considered operable at the time of diagnosis. The interval from diagnosis to death was only 3.8 months, while a period of 10.7 months elapsed from the onset of symptoms to diagnosis. The patient's delay in seeking medical advice was 6.4 months and the physician's delay in establishing the diagnosis was 4.3 months.

The clinical picture of primary bronchogenic carcinoma is mainly respiratory in character; the prominent symptoms are cough, chest pain, hemoptysis, dyspnea. Weight loss was a constant finding.

Fever and leucocytosis depend upon the presence of secondary pneumonitis. No significant anemia was noted in any of our cases.

The importance of tuberculin testing adults is re-emphasized. Nine of our patients had negative tuberculin test and should never have been considered as tuberculous.

The differential cell count of the pleural fluid revealed a marked lymphocytosis in three cases. Lymphocytosis is considered typical of tuberculous pleurisy with effusion and in these cases could mislead one to an erroneous conclusion.

Clubbing of the fingers is not an unusual finding in bronchogenic carcinoma.

The importance of roentgenograms, bronchoscopy, cytological examination of sputum and bronchial secretions and thoracotomy as diagnostic procedures are discussed.

RESUMEN

En un período de once años se observaron 47 casos de carcinoma broncogénico primario en el Sanatorio de Muirdale. Estos pacientes fueron enviados al sanatorio como casos de tuberculosis pulmonar. Se comprobó a 35 de los 47 casos mediante el examen autopsico o la biopsia y a uno por la presencia de células malignas en el derrame pleural. Se diagnosticó a 12 casos a base de los hallazgos clínicos, roentgenológicos y broncoscópicos.

Dos casos tenían tuberculosis pulmonar y también carcinoma broncogénico primario.

La edad media de nuestros pacientes fue de 55.4 años. Nuestro paciente más joven tenía 40 años y el más viejo 73 años de edad. La proporción de hombres a mujeres fue de 3 a 1.

De los casos comprobados, 14 fueron de tipo de célula escamosa, 14 carcinomas de célula no diferenciada, 3 adenocarcinomas y uno carcinoma de célula alveolar. No se pudo clasificar histológicamente a dos casos.

Lo importante del reconocimiento temprano del carcinoma broncogénico primario lo recalca el hecho de que a sólo cuatro de los 47 pacientes se les consideró operables cuando se les hizo el diagnóstico. El intervalo del diagnóstico a la muerte fue sólo 3.8 meses, mientras que un período de 10.7 meses transcurrió desde el comienzo de los síntomas hasta que se hizo el diagnóstico. La demora del paciente en consultar al médico fue 6.4 meses y la demora del médico en establecer el diagnóstico fue 4.3 meses.

El cuadro clínico del carcinoma broncogénico primario es principalmente de carácter respiratorio; los síntomas prominentes son: tos, dolor en el pecho, hemoptisis y disnea. La pérdida de peso fue un hallazgo constante.

La fiebre y la leucocitosis dependen de la presencia de neumonitis secundaria. No se notó anemia significativa en ninguno de nuestros casos.

Se recalca de nuevo la importancia de comprobar con tuberculina a los adultos. Nueve de nuestros pacientes eran negativos

a la tuberculina y nunca se les debería haber considerado ser tuberculosos.

La enumeración diferencial de las células del derrame pleural reveló decidida linfocitosis en tres casos. Se considera que la linfocitosis es típica de la pleuresía tuberculosa con derrame y en estos casos habría podido conducir a conclusiones erróneas.

El ensanchamiento de la punta de los dedos no es un hallazgo raro en el carcinoma broncogénico.

Se discute la importancia de los roentgenogramas, la broncoscopia, los exámenes citológicos del esputo y de las secreciones bronquiales y la toracotomía, como procedimientos diagnósticos.

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Pathogenesis of Pulmonary Atelectasis

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Before discussing the pathogenesis of atelectasis, three illustrative cases are described, each having a different aetiology. It is proposed to show later that even though the precipitating factor in each of the cases is different, the ultimate mechanism by which atelectasis is produced is essentially the same.

Case 1: Male, 26 years, was admitted to hospital for fever and cough of 10 days duration. The fever was continuous and ranged between 100 and 102° F. Respiration was not hurried. A diagnosis of bronchiolitis was made. A week later the condition of the patient became worse. The range of temperature was higher. His breathing also was a bit more hurried. On examination a triangular area of dullness in the left base behind, with bronchial breath sounds and a few moist sounds were found. X-ray picture (Fig. 1) showed a triangular opacity overlapping the left border of the heart. In the lateral view the opacity was found to be situated posteriorly. A diagnosis of left lower lobe atelectasis was made. As the total leucocyte count was 14,000, he was put on sulphapyridine, the temperature decreased by lysis. His signs and symptoms disappeared only eight weeks after admission. X-ray picture taken at that time showed that the opacity had disappeared (Fig. 2).

Case 2: Male, 33 years, gave a history of a fall during which the left side of his chest struck against a projecting stone. Pain was so severe that he had difficulty in breathing for some time. There was no external injury. He spat out a little blood-tinged mucous after the injury. The pain lasted for a week. Subsequently he developed cough with expectoration. He had no fever. A few moist sounds were heard in the left base, but no other physical signs could be elicited. An x-ray picture (Fig. 3), however, showed a narrow well defined triangular opacity overlapping the cardiac shadow in the left side. The diagnosis of left lower lobe atelectasis was confirmed by a lateral x-ray picture.

Case 3: Male, 24 years, had a fish bone admitted to the air passage while swallowing. He experienced difficulty in breathing and aching pain in the right side of the chest. Fever and cough started the next day. A few days later he began to expectorate purulent sputum. Examination revealed impaired resonance and bronchial breath sounds over the right base. X-ray picture showed a triangular opacity in the right cardiophrenic angle continuous with and obliterating the right border of the heart. Lateral view confirmed the diagnosis of right lower lobe atelectasis. Conservative treatment and postural drainage cleared up the condition in 6 weeks so the x-ray picture showed no opacity.

Intrapulmonary inflammation in the first, external thoracic injury in the second and frank bronchial obstruction by a foreign body in the third case brought about the same condition, namely lower lobe atelectasis. Inflammatory exudate in the first case in all probability produced multiple bronchiolar obstruction while haemorrhagic mucous secretion was the obstructing agent in the second case. The object of this paper is to show that bronchial or bronchiolar obstruction is the main contributing factor in the mechanism of collapse and that it brings about the condition in two entirely different ways.

Current Theories: The pathogenesis of pulmonary atelectasis has been a subject of discussion for over a century. Even the earliest observers like Reynaud (1835) and Hasse (1846) recognized the importance of bronchial obstruction in the aetiology of atelectasis. Gairdner (1850) regarded the blockage of bronchial tubes by retained secretion as the cause of collapse. Pasteur (1908) having seen massive collapse of the lung occurring during diphtheritic paralysis, postulated the theory of diaphragmatic paralysis to explain the occurrence of postoperative atelectasis. The experimental work of Briscoe (1919) appeared to confirm this theory. He pointed out that, in the supine position, the inspiratory movements of the diaphragm are ordinarily carried out by the crura

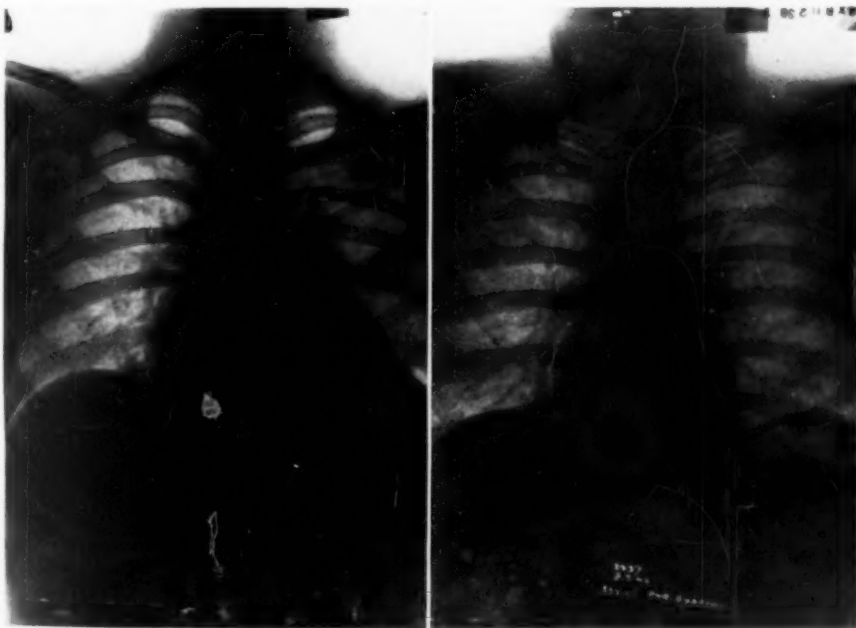


FIGURE 1

FIGURE 2

Figure 1, Case 1: Note the triangular opacity in the left cardiophrenic angle. Left dome of diaphragm raised.—*Figure 2, Case 1:* Note the disappearance of the opacity. Lower lobe has expanded.

and not by the costal attachment. Continued supine position might produce a certain degree of collapse which will be aggravated by irritation of the diaphragmatic pleura near the crura after abdominal operations. While Pasteur and Briscoe emphasized the importance of paralysis of respiratory muscles, Elliott and Dingley (1914) laid great stress on the importance of bronchial obstruction as the chief contributing factor.

A fresh stimulus to the study of massive collapse was given by Rose Bradford (1918) who observed a series of cases of collapse following nonpenetrating injuries to the chest during the Great War of 1914 to 1918. The chief explanation suggested by him was a reflex paralysis of the respiratory muscles. Those who have observed basal pulmonary collapse associated with infection of nasal sinus, also postulate reflex nervous stimulus as the causative mechanism. Coryllos and Birnbaum (1928) produced occlusion of the main bronchus by means of an air inflated balloon which caused pulmonary collapse in 6 hours. Jacobaeus (1930) noted massive collapse in the human subject within 10 minutes after introduction of lipiodol.

The most notable contribution to the knowledge of the subject has been made by Chevalier Jackson who emphasises the supreme

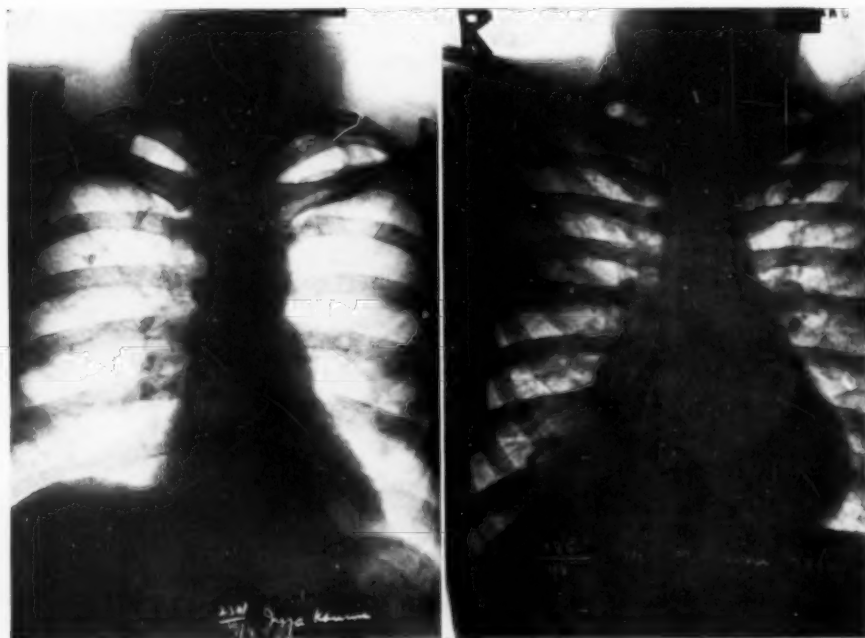


FIGURE 3

FIGURE 4

Figure 3, Case 2: Note the well marked triangular opacity inside the cardiac shadow in the left side.—Figure 4, Case 3: Note the triangular opacity in the right cardiophrenic angle. Outline intensified by touching.

importance of bronchial obstruction in producing atelectasis. Removal of a foreign body in the bronchus is followed by rapid disappearance of collapse. Jackson has shown that collapse in diphtheria is not due to paralysis of diaphragm but to obstruction of the bronchus by membrane and agglutinated mucous. When the obstruction was removed by the bronchoscope the symptoms and signs speedily cleared up. According to him cough reflex is the watch dog of the lungs and when that reflex fails the lumen becomes completely obstructed. It is interesting to note that as early as 1853 Gairdner gave the three chief causes of pulmonary collapse in infancy as, mucous in the bronchi, weakness of the respiratory muscles, and inability to cough.

Hilding (1944) dissatisfied with the explanation of bronchial obstruction, has put forward a fascinating theory based on some convincing experiments by which he has shown that loose mucous plugs can be moved up from the distal to the proximal ends of the bronchi and bronchioles through ciliary action. These mucous plugs act like pistons and as they move up one after the other columns of air are removed from the affected lobe until the latter is collapsed completely. The theory is ingenious. It cannot how-

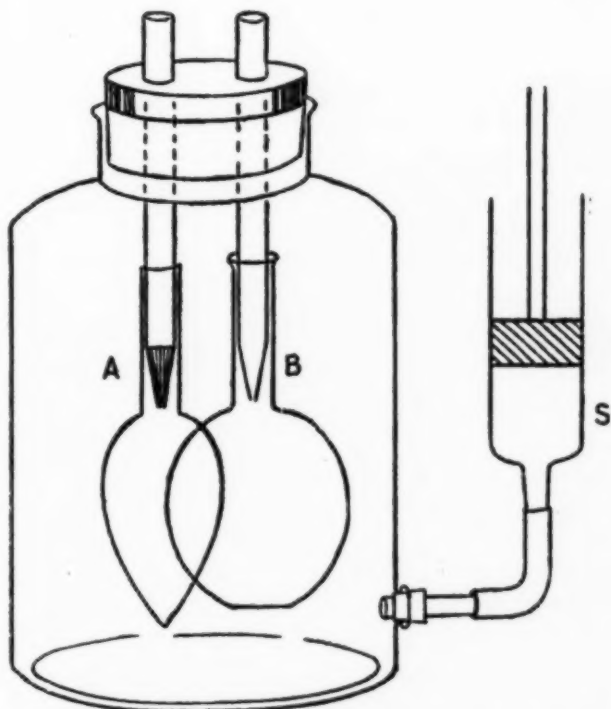


FIGURE 5: *Pulmonary Atelectasis*. Laboratory Experiment. Figure represents the state of the bladders at the termination of the experiment. Note 'A' in which the bladder is collapsed owing to presence of secretion in the glass tube. In 'B' the bladder is distended as there is no obstruction. 'S' represents the syringe.

ever explain the mechanism of collapse in all cases. His statement that air cannot be absorbed by the blood in the lung capillaries is disproved by the experimental production of collapse by complete obstruction to a bronchus. In such a case, air could have disappeared from the alveoli only by its being absorbed into the blood stream.

The mechanism of collapse in case of complete obstruction of the bronchi either intrabronchial as by foreign body or extra-bronchial as by tumour is easily understood. Air in the obstructed lobe has necessarily to get absorbed into the blood stream. Doubts and difficulties however arise when one tries to work out the process by which portions of lung become airless in nonpenetrating chest injuries, in pulmonary inflammations and after abdominal operations. When the theories so far advanced to explain the pathogenesis of massive atelectasis are analyzed they are found to fall into two broad groups, namely bronchial obstruction and respiratory paralysis. Paralysis chiefly of the diaphragm is brought about according to different theories in different ways. It might be a reflex mechanism, or an allergic response, or a true nerve paralysis as in diphtheria. The theory of respiratory paralysis as the sole cause of atelectasis cannot be substantiated. Respiratory paralysis no doubt will abolish any movement of air in the alveoli. Air in the alveoli in the natural course of events will be absorbed into the blood stream. It will however be replaced by outside air so long as there is no obstruction in the air passages. Hence the lung cannot collapse simply as a result of paralysis of respiratory muscles. Moreover massive collapse of the lung is not seen to occur after phrenic evulsion. Paralysis of the diaphragm produces only a relaxation of the lung and does not cause all the air to disappear. Besides, neither in postoperative conditions, nor after external chest injuries, do the respiratory muscles get so completely paralyzed as to cease functioning. Only reflex inhibition of respiratory movements and not total abolition, occurs in these conditions. In fact according to the theory propounded below, a certain amount of respiratory excursion is required to produce pulmonary atelectasis.

The protagonists of the bronchial obstruction theory, believe that complete blocking of the bronchi or bronchioles by thick mucous secretion and subsequent absorption of air from the alveoli into the blood stream are the processes concerned in the production of atelectasis. It has been seen no doubt that this is the mechanism in case of foreign body obstruction of the bronchi. I am, however, not convinced that mere mucous secretion however viscid it might be can produce complete bronchial or bronchiolar obstruction. Hilding has shown that through the muco-ciliary mechanism,

secretion can be moved up the bronchioles. Moreover, a fairly forcible current of air sufficient to dislodge mucous secretion passes to and fro during the process of respiration through the narrow bronchial or bronchiolar passage. Another point against the theory of complete obstruction is the length of time required to produce atelectasis. In Coryllos' experiment of bronchial occlusion it took nearly six hours to produce atelectasis.

Jacobaeus, on the other hand, observed atelectasis occurring within ten minutes after intrabronchial installation of lipiodol. The onset of posttraumatic and postoperative atelectasis is also equally sudden and rapid. It is obvious therefore that the process of absorption of air into the interalveolar blood stream cannot explain such rapid disappearance of air from the lung as it occurs in the above mentioned conditions. What then is the mechanism by which massive atelectasis is produced?

The theory which I wish to put forward as a rational and adequate explanation is substantiated by experiments performed on the human body immediately after death and on animals under anaesthesia, as well as by laboratory experiments. I agree with Jacobaeus and Jackson that bronchial or bronchiolar obstruction is a necessary condition to be satisfied before atelectasis occurs. Secretions in the bronchial tubes both in post-traumatic as well as postoperative conditions are the obstructing agents. Accumulation of secretion is no doubt caused by diminished respiratory excursion. If the process of rapid disappearance of air from the lung is to be understood the essential prerequisite of some respiratory movements should be granted. I contend that the mucous secretions in the bronchioles instead of producing complete obstruction act like ball-valves allowing air to get out from the lung during expiration but preventing air to get in during inspiration. The ball-valve-like action can readily be conceived because the bronchi are not of the same calibre throughout their length. The distal portions are narrower than the proximal portions. Hence it is easy to imagine how a plug of mucous can effectively block a bronchus or bronchiole as it is moved distally by the inspiratory air current and how on the other hand it will allow air to pass through when it is moved towards the broader proximal end. If for instance the lower lobe bronchus is blocked by a mucous plug some amount of air will be expelled during expiration as a result of the plug being moved to the broader proximal portion of the bronchus and thereby rendering it patent. During inspiration, however, air is not allowed to enter, and the lower lobe to that extent is partially collapsed. If a hundred cc. of air gets into one lung during each inspiration, all the hundred enters the upper lobe if the lower lobe bronchus is blocked. During the next expira-

tion as the intra-alveolar air pressure throughout the chest cavity is higher than the atmospheric pressure, air gets expelled from all the lobes irrespective of whether any one of them is partially collapsed. Hence more air passes out from the lower lobe during expiration than is replaced during inspiration. With every act of respiration the lower lobe becomes more and more collapsed and the process continues until it is completely airless. The mechanism is facilitated by the inherent tendency of the lung to shrink owing to its elasticity. It is quite conceivable how by this process atelectasis can be produced in a few minutes provided there is ball-valve-like obstruction to the bronchus and the integrity of respiratory excursion is maintained. Without respiratory movements rapid disappearance of air from a partially obstructed lobe cannot be produced. If a valvular opening in lung rupture can produce a tension pneumothorax, I see no reason why a ball-valve obstruction to the bronchus cannot produce rapid atelectasis. In fact it is not possible to conceive of any other way by which air can completely disappear from a lobe within the short period of ten minutes or even less. Absorption into the blood stream is out of the question as it has been shown by Ceryllos that it takes nearly six hours for atelectasis to be produced by complete obstruction, during which time air is absorbed into the blood.

Even the presence of liquid secretion in the bronchiole under favorable circumstances will contribute to establish a one-way traffic for the air which might bubble out through the fluid during expiration but is unable to get into the affected alveoli during inspiration. This is facilitated by the decreasing calibre of the distal portions of the bronchi and bronchioles. Each of these is in the shape of a narrow, more or less conical tube. If it contains fluid secretion the air from the alveoli attached to its narrow end can bubble through, but air coming from outside through the proximal end will not be allowed to pass as the fluid will be driven to the narrow distal end where it will form an effective block for the air. In the case of multiple lobular atelectasis after drowning, described previously by the writer (1941), sea-water acted as the obstructing medium and evidently operated by the above described mechanism. It is obvious that not only should there be an obstructing agent in the respiratory passages but the respiratory movements should be maintained as well.

The following experiments were performed to substantiate the theory described above:

- 1) The first experiment was on a human body immediately after death. Materials required were previously prepared as the time of death was anticipated. The trachea was opened and a rubber tube introduced into the right bronchus. Twenty cc. of an

oil emulsion of the consistency of lipiodol was introduced through the tube. Artificial respiration by the writer's method (1945) was given for five minutes. The trachea was then plugged air-tight with a cork and the chest opened in the usual manner. The right lower lobe was found to be distinctly, though partially collapsed, while the left lung and right upper lobes remained distended owing to the trachea being plugged. Evidently the emulsion had gone into the right lower lobe bronchus and produced the necessary block. With the help of artificial respiration and blockage of the bronchus collapse of the lower lobe was obtained.

Keeping the thoracic structures in situ the left bronchus was opened and two rubber tubes were introduced into the upper and lower lobe bronchi respectively and pushed so as to make them fixed inside. The free ends of the tubes were connected to the limbs of a Y-shaped nozzle whose opposite end was connected to the exit end of a Higginson's syringe. Air was pumped in, to make the lobes partially distended. The tube to the lower lobe bronchus was disconnected from the nozzle and after a few cc. of soft soap emulsion was introduced, it was reconnected. Air was pumped in with the aid of the syringe. It was found that while the upper lobe was getting distended the lower lobe remained as it was. The Higginson's syringe was disconnected and uniform pressure was applied to both of the lobes, which collapsed. When more air was pumped in the upper lobe alone expanded while the lower lobe remained collapsed occupying a posterior position in the chest cavity.

2) A simple laboratory experiment was designed to show the mechanical nature of the process involved in the production of atelectasis. A large wide-mouthed jar with a narrow side-opening near the bottom was chosen. It was fitted with a cork with two perforations through which two glass tubes were introduced. Each tube tapered to a capillary end. A small football bladder was fitted to each of the tubes so that the bladders remained suspended inside the jar. The lower opening in the jar was closed with a cork to which a glass tube was fitted. The outer end of the glass tube was connected to rubber tubing to whose free end was fitted the lateral nozzle of a Potain's aspirator. The air from the jar was aspirated to such an extent as to produce moderate distension of the bladders. The aspirator was then removed and the nozzle of an ear syringe was fitted to the rubber tube. By working the piston to and fro a bellows action could be produced so as to increase or decrease the pressure of air inside the jar to an equal measure each time. The result was, the bladders contracted or expanded as the pressure of the air inside the jar increased or decreased. The jar represented the chest and the

bladders represented two lobes of a lung. The glass tubes fitted to the bladders represented the bronchi.

Into one of the glass tubes was introduced a small mucous plug from the sputum of a patient. The syringe was worked slowly at the rate of 18 per minute. It was found that the bladder connected to the glass tube into which the mucous plug was introduced contracted each time when air was pumped into the jar, but failed to expand when the process was reversed. The result was the bladder shrank in size while the other bladder expanded more and more.

The experiment was repeated with a viscid fluid inside one of the glass tubes. It was not successful as it was found that the fluid was gradually getting aspirated into the bladder through the capillary opening. The tubes being vertical, the action of gravity helped in driving the fluid through. In order to overcome this difficulty the jar was kept slanting about 5 degrees from the horizontal. This would have more or less corresponded to the recumbent position of a patient in bed. As the action of gravity was almost overcome in this manner, the experiment succeeded. The air from the bladder bubbled out through the fluid during the process of contraction. The fluid however effectively blocked the passage of air back into the bladder. The same results as in the experiment with the mucous plug were obtained.

It has been conclusively proved by the above experiments that obstruction to the bronchi either with semisolid or fluid material, recumbent posture and shallow respiration are the necessary and sufficient conditions to produce atelectasis of the lung.

3) A dog was anaesthetized. Chloroform was used so as to produce shallow respiration. The trachea was opened at the lowest possible level and a rubber catheter was introduced into the right bronchus, ten cc. of viscid sputum were introduced through the catheter. The dog was kept under for another ten minutes, during which period shallow respiration was maintained. The dog was killed by deepening the anaesthesia. The trachea was firmly plugged with a cork so as to allow no air to escape from the lungs consequent on their shrinking during opening of the chest cavity. On post-mortem it was found that the lower lobe of the right lung was almost completely collapsed.

All the experiments described above conclusively substantiate the theory propounded in this paper. The pathogenesis of atelectasis can be briefly summarized as follows: Taking postoperative atelectasis as an example, the process starts with accumulation of secretion in the bronchi and/or bronchioles. This is facilitated by diminished respiratory movements and temporary dysfunction of the muco-ciliary mechanism. Owing to progressive distal nar-

rowing of the bronchioles, the secretion effectively blocks the air getting into the alveoli during inspiration, but allows it to escape outside during expiration. This process therefore depends on the integrity of the respiratory movements however shallow they might be. After repeated acts of respiration the affected lobe becomes collapsed.

Apart from post-anaesthetic conditions restriction of respiratory movements can be produced through pain, either pleuritic or post-traumatic. Excessive secretion necessary for blockage can be produced either by bronchiolar inflammation as in the first case or posttraumatic haemorrhage as in the second. The mode of production of atelectasis in the third case was similar to that in Coryllos experiment, namely complete bronchial obstruction and subsequent absorption of air into the blood stream. The more frequent occurrence of lower lobe atelectasis particularly in post-operative conditions, is due to several factors. The whole of the posterior surface of the lower lobe is in contact with the back of the chest and practically the whole of the diaphragmatic surface of the lung is formed by the lower lobe. When the back is fixed in the recumbent position, if the diaphragmatic movement also is restricted either through post-anaesthetic shallow breathing or through tight abdominal bandaging, the respiratory excursions of the lower lobe will be rendered relatively smaller than that of the upper lobe. Hence stasis of secretion occurs more easily in the lower lobe bronchioles. Moreover the lie, direction and inclination of the lower lobe bronchus and its branches are more favorable to the production of ball-valve action of the secretion inside them. Lower lobe atelectasis is therefore less likely to happen if the patient, after operation, is propped up or turned to one side or the other. Perhaps by keeping the patient in the Trendelenburg position until normal breathing is established, pulmonary atelectasis might be prevented, as it will prevent accumulation of secretion in the lower reaches of the bronchioles.

SUMMARY

- 1) Three cases of lower lobe atelectasis are described.
- 2) A short review of the available literature on the pathogenesis is given.
- 3) The writer is of the opinion that establishment of one-way traffic for the air in the bronchioles by the presence of secretion inside is the cause of pulmonary atelectasis. Respiratory movements are none the less necessary.
- 4) Experiments are described to substantiate the theory.
- 5) Reasons for relative frequency of lower lobe atelectasis are cited.

RESUMEN

- 1) Se describen tres casos de atelectasia del lóbulo inferior.
- 2) Se presenta una corta revista de la literatura obtenible sobre la patogenia de este estado.
- 3) El autor opina que el movimiento del aire dentro de los bronquiolos, debido a la presencia de secreciones, es la causa de la atelectasia pulmonar. Sin embargo, los movimientos respiratorios también son necesarios.
- 4) Se describen experimentos que verifican esta teoría.
- 5) Se citan varias razones para explicar la relativa frecuencia de la atelectasia del lóbulo inferior.

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Lipoid Pneumonia in Neuropsychiatric and Debilitated Patients

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Lipoid pneumonia is a relatively recent clinical entity which has attracted much attention in medical literature in the past two decades and during the last year the dangers associated with continued and excessive use of mineral oil have been stressed.³ Formerly believed to be a disease among children following the use of oily nose drops, the condition is not as uncommon in adults as was previously thought.⁴

The four cases presented in this paper were collected from seventy-three consecutive autopsies performed at this hospital. It is not surprising that lipoid pneumonia should occur with relative frequency in neuropsychiatric patients, particularly, where intellectual and emotional regression to the infantile level has taken place. Feedings and medications can be administered to these patients often only when the greatest difficulty and the aspiration of oily medications is a constant hazard. This is especially true in advanced bulbar palsies of various types where deglutition has been impaired and in those patients who are bedridden and confined to wheel-chairs. The inactive patient is a constant feeding problem and often has sluggish, irregular bowel movements and is frequently in need of laxatives. Mineral oil and cascara have been the favorite medications for this purpose over a period of years and were formerly considered innocuous; however, it has been amply pointed out by Sweeny¹⁰ that mineral oil is often the offender in lipoid pneumonia. In his compilation of one hundred and thirty-one adult cases he showed that the use of mineral oil as a laxative accounted for one half the series.

REPORT OF CASES

Case 1: J. T. M., a 52 year old white male was admitted to the hospital in April 1939, in the advanced stage of postencephalitic Parkinson's disease, with marked impairment of locomotion, pill-rolling tremor, mask-like facies, and drooling at the mouth. Hospitalization under close supervision was necessary to assist him in eating, bathing, and walking around the ward and grounds. Medication consisted of atropine, hyoscine and various vitamin preparations. Early in the course of hospitalization it

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was noted that the patient's bowel movements were irregular and mineral oil was given regularly once or twice a week.

In January 1941, it was noted that the patient was becoming frequently subject to "colds." At this time he developed what was interpreted as a bronchopneumonia. Mineral oil was continued in doses of one ounce twice a week. In April 1942, a routine chest plate showed only slight peribronchial thickening, more marked in the right lung, which was interpreted as a low grade bronchitis.

In December 1942, the patient developed his second bout of pneumonia. The pneumonia lasted four days and the patient made an uneventful recovery. Following this he developed a chronic cough.

In January 1944, the patient developed his third attack of bronchopneumonia with an intermittent fever, sometimes reaching 105 degrees F. The patient was critically ill but recovered after three weeks. X-ray film at this time revealed moderate peribronchial infiltration confined mostly to the right middle and lower lobes. It is of interest to note that in April 1946, two years and three months later, while the patient was supposedly completely well, a routine chest film revealed peribronchial infiltration at the right base and right middle lobe, similar to film taken during previous illness.

The terminal illness began one year later with weakness, anorexia, high fever, and a rapid pulse. Chest films taken at this time showed peribronchial infiltration involving primarily the lower lobes of both lungs, but more marked on the right where the upper lobe was also involved. Rales developed in both bases and in spite of penicillin, fluids and oxygen therapy, the patient expired.

Necropsy findings were essentially negative except for the lungs which were free in the pleural cavities and exhibited dark red color and boggy character characteristic of an advanced pneumonic process with consolidation. Microscopic examination of the lung tissue revealed masses of polymorphonuclear leukocytes and debris filling the alveoli and bronchioles with a number of phagocytes filled with lipid droplets.

Case 2: J. H., a 41 year old white male entered the hospital in April 1934. A diagnosis of Huntington's chorea was made and his course of hospitalization was that of a typical case with progressive mental enfeeblement and increase in neurological symptoms. In October 1943, it was first noted that the patient had difficulty in swallowing food and medications. Shortly thereafter his bowel movements became irregular and mineral oil and cascara were administered at regular intervals. Mineral oil and cascara were given once a week every week for the last three years of his life.

The patient continued to fall and one month before death developed a low grade fever and cough with moderate cyanosis and dyspnea. A chest film at this time revealed a diffuse peribronchial thickening involving primarily the right middle and lower lobes with evidence of infiltration (Fig. 1). In spite of specific and supportive therapy the patient expired.

At necropsy the right lung appeared to be partially collapsed and lay in 800 cc. of hemolized blood in the pleural cavity. The entire middle lobe was dense and firm and on section it was yellowish and increased in consistency with no increase in fluid. There was a fibrous exudate over the pleural surface with a few broken adhesive tags. The left lung was bound down by firm adhesions laterally and the lower three fourths

showed decreased crepitus and was boggy and dark red; on section fluid was markedly increased with purulent areas. The pleural cavity was empty. Sections of the brain showed atrophy of the caudate nucleus and other findings characteristic of Huntington's chorea.

Microscopic study of lung sections showed pus cells in many alveoli, often forming small abscesses. Macrophages filled with lipid material or droplets, predominated in other areas. There was considerable fibrosis with thickening of the alveolar wall (Fig. 2).

Case 3: S. S., a 65 year old white male was admitted to the hospital with a right cerebral thrombosis. A few days after admission it was noted that the patient was constipated. Petrogalar and phenolphthalein were administered. For the next seven months the patient received these drugs in one ounce doses one to three times a week. The orders were then changed to mineral oil and cascara and this was administered once or twice a week for three months.

Five months later the patient developed his first attack of "pneumonia." At that time he complained of a pain in the left chest. He had a low grade fever, never exceeding 100.2 degrees F. rectally. The chest findings were completely negative. A chest plate at that time was reported as normal. The patient was treated symptomatically with some improvement. He developed a hacking chronic cough productive of thick, white sputum. Six months later he again developed a pain in the left chest and a "cold." X-ray plate at this time showed "marked accentuation of the bronchovascular tree" and "increased density in the left

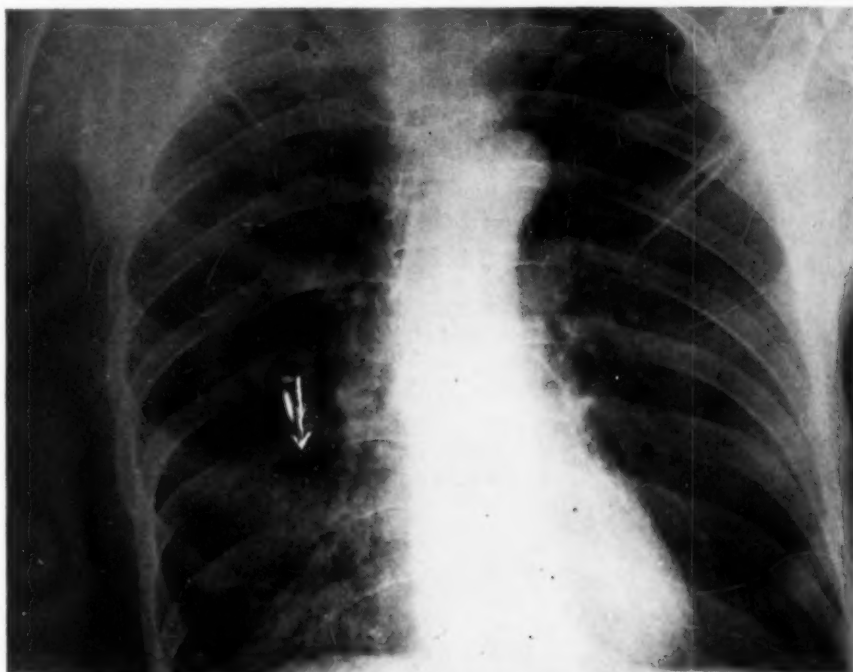


FIGURE 1: Chest plate of patient in Case II. Note peribronchial thickening in region of right cardiophrenic angle. There is a soft area of infiltration seen in the central portion of right lower lobe (arrow).

lower lobe suggesting pneumonitis." The patient recovered from this illness but his cough increased in frequency and severity.

Eight months later the patient had another chest plate because of chronic cough and low grade fever. This was read as "chronic bronchitis" and "slight infiltration in left lower lobe suggesting pneumonitis."

Four months before death, while the patient was considered asymptomatic, a routine chest plate was done during a tuberculosis survey. This plate was identical with those taken during the episodes of "pneumonia" showing an increase in bronchovascular markings with a similar area of infiltration in left lower lobe.

It is of interest to note that no oily substances were administered to the patient thirty months prior to his death. In spite of this the patient's course was downhill. He developed low grade fever, cyanosis, signs of respiratory embarrassment, and finally expired in spite of supportive therapy.

The pulmonic pathological changes were of interest despite the apparent demise of the patient from a coronary accident. The lungs were free in the pleural cavities which were empty. Anthracosis was present, grade 2. The weight of the left lung was 480 grams and it contained many poorly outlined, rubbery nodules which varied between 1 cm. and 4.5 cm. in diameter. They were grey against the more or less normal lung tissue which served as a pink background. These nodules were scattered throughout all the lobes but were more numerous in the right lung which weighed 575 grams. The right lower lobe was boggy and dark red in color with a marked increase in consistency.

Microscopically the lung revealed a fibrous thickening of the alveolar

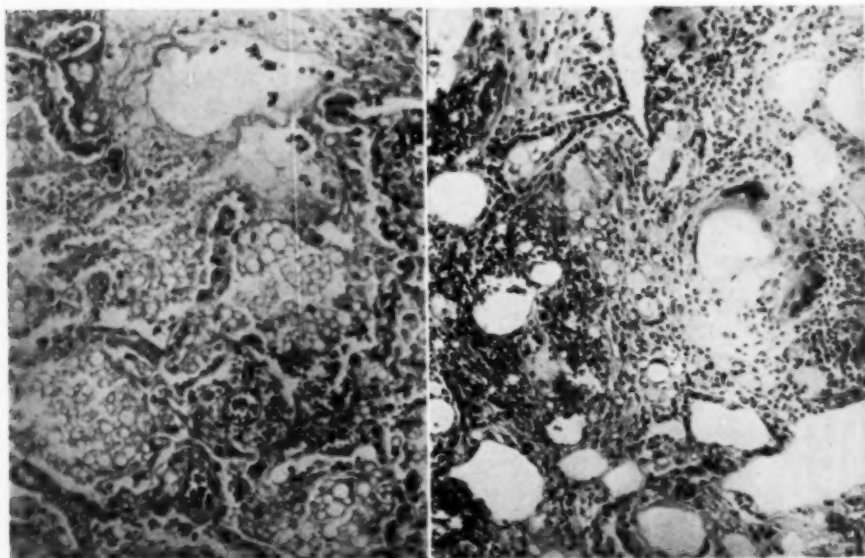


FIGURE 2

FIGURE 3

Figure 2: Lung section from Case II. The alveoli present a foamy appearance due to lipid-filled macrophages.—*Figure 3:* Section of lung from Case III. The alveolar structure has been destroyed by proliferating fibrous tissue. There are extensive lymphocytic aggregations. There are numerous lipid spaces in the connective tissue and giant cells have formed about some of the larger droplets of oil.

walls with obliteration of many alveoli due to the connective tissue proliferation. The connective tissue and alveoli contained numerous foreign body giant cells (Fig. 3), many of these formed about circular clear spaces of varying dimensions which were assumed to be lipid or oil droplets and which were demonstrated as such in microscopic preparations stained with fat stains. Also present were many macrophages filled with lipid droplets.

Case 4: C. S., a 49 year old white male was admitted to this hospital in January 1944. The patient's grandmother, father, two sisters and two brothers had had Huntington's chorea. The patient developed choreiform movements twenty-two years prior to admission. These movements became progressively worse. He grew extremely irritable, depressed, and his reasoning and judgment became defective. He was admitted to this hospital for observation. Physical examination was essentially negative. Neurological examination revealed many choreiform, isolated and uncoordinated movements of all extremities. His speech was slurred and he had much difficulty in swallowing. The patient was given thiamin and nicotinic acid. Cod-liver oil was given twice a day, every day for forty-two days. Sixteen months after admission the patient developed a slight cough and began to run a low grade fever, never exceeding 100.6 degrees F. rectally. This condition lasted about ten days and cleared spontaneously without treatment. The patient got along fairly well until April of 1947 when he developed a chronic, hacking cough which persisted until the time of death. One week before death the patient developed a low grade fever and his cough increased. Coarse rales were heard at both bases. His color was ashen gray and the lips cyanotic. Supportive treatment was of no avail and the patient expired. No oily medications had been administered to this patient for thirty-one months previous to death. X-ray plates taken at intervals during hospitalization were unsatisfactory because of inability of patient to remain quiet enough for the exposure.

At necropsy the most pertinent findings were those of a bronchopneumonia. Of added interest was atrophy of the caudate nucleus with consequent internal hydrocephalus, so characteristic of Huntington's chorea. The lungs were small, the right weighing 330 grams. The upper lobe was aerated and pink, the lower lobes were darker and crepitus was absent in these two lobes. Fluid was slightly increased on cross section and froth decreased. The left lung weighed 605 grams, was reddish-brown on the pleural surface and on section it was firm and noncrepitant and was apparently the result of a well established pneumonic process. Microscopic examination of the lungs revealed many lipid-filled macrophages in the alveoli with some monocytes and polymorphonuclear leukocytes.

Incidence

The reports of the incidence of lipid pneumonia have varied and in many instances have included the type that occurs commonly in infants. This would tend to make the cases more numerous; however, in the last two decades, following the work of Laughlen⁶ in 1923, the use of oily nose drops in children was widely and generally condemned so that recent studies should show but very few cases in this age group. Pinkerton⁹ in 1927,

noted six cases in 290 consecutive necropsies, an incidence of 2 per cent. Ikeda⁵ in 1935, found an incidence of 7 per cent in children, and encountered five adult cases in an unrecorded series of necropsies, but no single instance in a series of thousands performed before 1932. Freiman et al⁴ in 1940, found 1.2 per cent in a series of 3500 necropsies in adults and Cannon² recorded a percentage almost similar in 2000 adults. The four cases presented represent approximately 5.4 per cent in a consecutive series of necropsies.

Diagnosis and Clinical Course

It has been estimated that approximately one fourth of the cases are considered asymptomatic as far as the lipoid pneumonia is concerned, but often a careful review of the history following necropsy will reveal that what appeared to be a spontaneous bout of terminal pneumonia was actually the last of a series of pneumonic attacks over a long period of time which were superimposed on the fertile soil of a long-standing lipoid affair. A history of repeated respiratory and pulmonic infections, with a chronic cough between bouts, particularly in those individuals taking large amounts of mineral oil, cod-liver oil, or oil-agar preparations, should always suggest a lipoid pneumonic process as a predisposing factor and serial x-ray films taken over a period of time should lend further support to and increase the incidence of antemortem diagnosis. Patients with dysphagia are particularly prone to this disorder as well as the debilitated and bedridden patient who is constipated and who often is a feeding problem as well. The presence of oil in the sputum after the intake of oil, milk, cream or other fats have been restricted for some time is often of diagnostic importance, either by centrifugalization and the use of fat stains, or by observing the oil drops on a bit of cigarette or tissue paper immersed in the specimen. Aspiration biopsy of the lung has also been suggested by Nathanson and his associates⁸ but one must consider that one might readily strike relatively normal areas due to the patchy distribution.

Roentgenological Findings

Moel and Taylor⁷ aptly called attention to the main roentgen findings in oil aspiration pneumonia. Early involvement manifests itself as an increase in the bronchial markings, usually on the right. These linear striations are often interpreted as bronchiectasis. The periphery of the lung is not involved. Later the shadows may become confluent and nodular, and they may have an irregular border which suggests the infiltrating nature of a malignancy (Fig. 1). The hilar shadows may or may not be en-

larged on the side of involvement. Parafinomas may occur forming a large oval mass of smooth outline usually located close to the hilar region.

The single most important factor in the x-ray diagnosis of this disease is the persistent nature of the lesions. Although the findings in the lung fields may be altered for brief periods by superimposed pulmonary infections, the underlying disease is always present and seen in interim films even though the patient may appear clinically asymptomatic at that time. The chief findings may show some progression even though the administration of oily substances is stopped (as in Case IV). This is probably due either to continued superimposed low grade infections at the site of involvement or to the proliferative nature of the disease.

X-ray findings are not specific and may be mistaken for bronchiectasis, tuberculosis, silicosis, broncholitis obliterans, and a host of other conditions. It is necessary to correlate the history, clinical findings, and chest plate in order to arrive at an early correct diagnosis.

Pathological Findings

The gross and microscopic pathological findings are characteristic in lipoid pneumonia, but vary due to the nature of the lipoid aspirated, the amount present in the lungs, and the length of time it has acted upon the lung tissue. The term "lipoid pneumonia" is used in this paper because it has become well established by long usage, actually it is a misnomer and the suggested names, such as pneumolipoidosis,¹ are far more descriptive. The victims of this disease die from a pneumonia or pneumonitis, the lipoid reaction merely acts as a fertile background and constant and irrevocable predisposing factor.

Grossly the lungs are vaguely nodular and on section present rubbery nodules of varying diameters, which in addition to their typical elasticity, have a rather uncommon gray-yellow or gray-brown coloration which is poorly outlined and does not resemble any other process. In two of the cases presented lipoid pneumonia was diagnosed from the gross cut sections of the lung prior to verification by microscopic study.

Microscopically the mineral oil droplets are absorbed by macrophages which may fill the alveoli and produce a foamy appearance (Fig. 2). If the affair is of long standing or the oil is less bland, some fibrous tissue reaction results but in many instances the alveolar walls appear essentially normal and are unaffected by their contents. In Case III the mineral oil has served in part as a vehicle for phenolphthalein, a drug whose cathartic action depends on its irritative effect on the bowel mucosa. In this case

the connective tissue reaction is far more intense with a chronic inflammatory affair associated with masses of lymphocytes and giant cells forming about the oil droplets. To our knowledge the baleful effect of combinations of oil and phenolphthalein, when introduced into the lung, has not been previously described.

Treatment

The treatment of lipoid pneumonia is entirely prophylactic. It seems apparent from this study that oily medications are contraindicated in neuropsychiatric and debilitated patients. This is unequivocal in any patient with bulbar involvement. Substitution of non-oily laxatives for mineral oil should be easily accomplished with the wide field of laxatives from which to choose. Fat-soluble vitamins are better given in capsule form to these patients. It must be pointed out that mineral and animal oils in the lungs are not absorbed and despite discontinuance of the oil the clinical and x-ray findings will persist and in some instances progress as illustrated in Case III.

SUMMARY

1) Four cases of lipoid pneumonia in neuropsychiatric and debilitated patients are presented which represented 5.4 per cent in a series of seventy-three autopsies.

2) The diagnosis is based upon a history of ingestion of oily substances, repeated bouts of pneumonia, the demonstration of oily droplets in the sputum following a lipid-free diet, and the x-ray findings.

3) The x-ray findings are not specific but they are characteristic in the sense that they are persistent even though the patient may be asymptomatic.

4) Pathologically the gross appearance of the lungs is highly suggestive and the microscopic findings are specific.

5) A particularly destructive type of lipoid pneumonia is demonstrated when the mineral oil is employed as a vehicle for phenolphthalein.

6) Treatment consists primarily in prophylaxis.

RESUMEN

1) Se presentan cuatro casos de neumonía lipoidea en pacientes neuropsiquiátricos y debilitados, que representan el 5.4 por ciento de una serie de setenta y tres autopsias.

2) Se basó el diagnóstico en la historia de la ingestión de sustancias aceitosas, repetidos ataques de neumonía, la demostración de gotitas de aceite en el esputo subsiguiente a una dieta libre de lípidos y los hallazgos radiográficos.

3) Los hallazgos radiográficos no son específicos, pero son característicos en el sentido de que persisten aunque el paciente no tenga síntomas.

4) Patológicamente el aspecto macroscópico de los pulmones es muy sugestivo y los hallazgos microscópicos son específicos.

5) Se demuestra un tipo de neumonía lipoidea particularmente destructiva que resulta cuando se emplea el aceite mineral como vehículo de la fenoltalina.

6) El tratamiento consiste principalmente de la profilaxia.

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Mediastinal Tumors and Cysts

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From a rather extensive review of the literature^{1,2} and an analysis of the case records of patients subjected to operation for mediastinal tumors and cysts the following particular impressions were gained.

These neoplasms are relatively infrequent. The most common primary types are those of the thymus and those arising from lymphatic tissues, dermoids and teratomas, and the neurogenous tumors. The cystic dermoids are more frequent than the more solid teratomas. Tumors of the sympathetic nerves are the most common type of neurogenous tumors. Bronchogenic cysts, fibromas, lipomas and intrathoracic goiters apparently occur somewhat less frequently than the above, while other tumors and cysts of this region seem to be exceedingly rare.

The majority of the tumors are malignant and many of the benign ones are potentially malignant. It would appear that the majority of the tumors occurring in the mediastinum are those originating from lymphatic tissue and secondary malignant tumors which are not as yet amendable by surgical treatment. The other tumors and cysts are principally benign, though a group of primary malignant tumors other than of lymphatic origin occur in this region. Primary carcinoma is apparently less frequent than primary sarcoma but secondary sarcoma is rare in the mediastinum. Secondary carcinomas in the mediastinum occur most frequently from primary tumors elsewhere in the chest.

The majority of thymic tumors are malignant, while many of the benign types, as well as an occasional malignant one, are associated with myasthenia gravis. The incidence of malignant tumors is estimated to be between 10 and 20 per cent in neurogenous tumors as well as in dermoids and teratomas. The incidence is higher in the more solid teratomas than in the more cystic dermoids. A somewhat higher frequency of malignant degeneration is thought to occur in fibromas and malignant degeneration is noted in other tumors of connective tissue. A malignant change in cysts other than dermoids would appear to be unusual but is occasionally noted in intrathoracic goiter (about 2 per cent).

Small cell lymphosarcomas and gastro-enterogenous cysts occur clinically, as a rule, in infants and young children while malignant neurogenous tumors, lymphangiomas and bronchogenic cysts are

usually noted before the age of 20 years. Dermoid cysts and teratomas, though often noted in the above age group, are most frequently observed between the ages of 20 and 40, as are benign thymic tumors, benign neurogenous tumors, most benign tumors of connective tissue, intrathoracic goiters, parathyroid adenomas, malignant tumors of lymphatic tissue, sarcomas of the thymus, and other sarcomas. Fibromas, carcinomas of the thymus, and other carcinomas are usually seen after the age of 40 years. The majority of mediastinal tumors and cysts apparently occur before middle age and many are congenital.

Malignant thymic tumors, large cell lymphosarcomas and Hodgkin's disease apparently occur somewhat more frequently in males, while neurofibromas, intrathoracic goiters, and parathyroid adenomas are noted more often in females. There appears to be no particular sex predilection in the other tumors and cysts that is discernable as yet.

There are some signs and symptoms which, if present, are suggestive of the type of tumor and cyst; such as those of myasthenia gravis in benign thymomas, and the marked respiratory distress in the presence of malignant thymic tumors or intrathoracic goiters, and the progressive involvement of nearly all the mediastinal structures and lymphatic tissues in lymphoblastomas. Other symptoms and signs that may indicate the type of tumor are those of nerve involvement, usually before other symptoms are prominent, in neurogenous tumors; the insidious onset with episodes of symptoms, expectoration of hair or sebaceous material in dermoid cysts, as well as symptoms of suppuration in these and bronchogenic cysts. Skin ulceration and activity of the drainage, or associated abdominal symptoms may be noted in gastro-enterogenous cysts. The expectoration of hooklets and scolices as well as the use of indicative tests may be of aid in the diagnosis of echinococcic cysts. Other suggestive symptoms and signs are the apparent external thoracic cage deformity in cartilaginous tumors, and those of hyperthyroidism with a palpable rising nodular mass on swallowing or coughing in intrathoracic goiter. Benign neurogenous tumors, aberrant bronchogenic cysts, pericardial coelomic cysts, fibromas, and those located in the posterior mediastinum are apt to be fairly "silent." In malignant tumors the symptoms are usually progressive and more severe with involvement of the mediastinal structures, and metastasis may be present. Symptoms of long duration are more suggestive of benign tumors. The symptoms in general appear to depend on the location, size and character of the tumor. There may be general signs and symptoms of mediastinal compression and those of implication of specific structures.

Thymic tumors, tumors of lymphatic origin, dermoids and teratomas, pericardial coelomic cysts, lymphangiomas, and apparently fibromas are usually located in the anterior mediastinum. Neurogenous tumors, xanthomas, gastro-enterogenous cysts, and echinococcic cysts are usually noted in the posterior mediastinum. Bronchogenic cysts, hemangiomas, cartilaginous tumors, lipomas, and fibromas, however, may be found anywhere in the mediastinum. Bronchogenic and gastro-enterogenous cysts are frequently located in the right side of the mediastinum. Apparently bronchogenic cysts, tumors of lymphatic tissue, and secondary malignant tumors are frequently seen near the central mediastinum on roentgenograms made of the lateral view of this region.

Certain roentgenologic findings other than the location of the neoplasm, when present, are also suggestive of the type of tumor; such as a flattened disc on the lateral roentgenogram in the case of thymic tumors. Irregular, poorly defined, lobulated borders are usually noted in malignant tumors of lymphatic tissues, though the mass may be somewhat more defined in Hodgkin's disease. Bony erosion of the vertebrae and adjacent ribs may be seen in the presence of benign neurogenous tumors. A smooth, rounded density or the presence of air and a fluid level usually indicates a cyst, while the line formed by two fluids of different density suggests a dermoid cyst. A well-defined lobulated mass which may contain tooth buds frequently denotes a teratoma, while multiple shadows in a circumscribed density suggests a hemangioma or lymphangioma. A lessened peripheral density may indicate a lipoma, while attachment of a mass to skeletal structures is suggestive of cartilaginous and bony tumors. A high wedge-shaped mass, particularly one showing movement on swallowing, is often observed in intrathoracic goiter. A well-defined, smooth, rounded density is suggestive of benign tumor or cyst but a malignant tumor may also present this characteristic. A diffuse, irregular shadow, especially with evidence of bony destruction of the infiltrative type, is suggestive of a malignant tumor. Some benign tumors may simulate this picture, particularly if a complicating infection is present, or may even be hidden by such a condition. The determination of the presence of a mediastinal mass, where possible, is aided by the use of special views and roentgenologic techniques, including the use of contrast media to gain the relationship of structures. Roentgen therapy except as a diagnostic measure where a lymphoblastoma is suspected and as a palliative measure, appears to be of little value.

Broncho-esophagoscopy, in most instances, is of little direct diagnostic value except by inference in the case of mediastinal tumors and cysts but is a definite aid in the differential diagnosis

of many other intrathoracic lesions. Exploratory thoracotomy appears to be usually preferable to pneumothorax and thoracoscopy as a diagnostic measure. This is because of the dangers and complications of the latter procedure, particularly if adhesions are present; moreover the results are not conclusive in most instances nor is the pneumothorax of much compensatory value. With modern methods of anesthesia, the danger of thoracotomy alone is minimal and an operable tumor can be removed at the same time. Needle aspiration for biopsy purposes in the case of mediastinal neoplasms holds considerable danger because of the proximity of vital organs. If used, it should be reserved for lesions in which there is a question of operability and where the neoplasms are adherent to the chest wall. Material for biopsy otherwise can be obtained from those few mediastinal tumors which present themselves in the chest wall or from an external metastasis.

It would seem that practically any tumor or cyst in the mediastinum should be explored and the neoplasm removed if possible providing there is no metastasis, irremovable invasion, lymphoblastoma or secondary malignant tumor, and the patient's condition permits operation. Surgery is indicated on account of the doubt in many instances as to the character of the neoplasm and because of the incidence of malignant types present within the mediastinum or thorax. Operation is also indicated because of the frequent growth of these neoplasms with consequent symptoms and because of the frequency of associated infection with its complications. The primary consideration would appear to be whether the intrathoracic tumor were excisable or not. Large tumors as such should not deter attempted removal, though some cases present the problems of rapid postoperative adjustment of the cardio-respiratory function following removal inasmuch as gradual compensation of function occurs during the growth of such neoplasms. The surgical approach is governed to a large extent by the location and size of the neoplasm. Such routes as the sternal-splitting procedure for tumors of the thymus may be used to advantage in some cases. Variances of the posterolateral incision and a transpleural approach through the rib bed, however, apparently offer greater accessibility and are satisfactory in most instances. In this case, measures must be taken to prevent tension pneumothorax and to bring about expansion of the lung with obliteration of the pleural space (to prevent infection) in the immediate postoperative period. This may be accomplished either by drainage or aspiration as indicated.

The overall mortality of patients subjected to operation in the past is estimated to be about 30 per cent. A fair proportion of the

cases forming the basis of the above estimate were operated on before the period of rapid progress in thoracic surgery. The operative mortality is lower for some neoplasms, even less than 5 per cent, particularly in benign tumors and cysts, with the exception of the gastro-enterogenous group. The direct operative mortality has been considerably reduced in recent years. The majority of deaths occur in those with malignant tumors and where complications, particularly infection, are present. The results are also much better when it is possible to carry out a primary excision of the tumor or cyst. Better management of these cases in recent years is indicated not only by the results, but by the decrease in the hospitalization period required and the decrease in the duration of symptoms of those admitted for operation. There is some evidence that wider use of roentgenologic surveys of the chest may bring about earlier diagnosis—before complications occur—with resultant improved results from surgical treatment.

RESUMEN

Mediante ciertas observaciones se puede obtener alguna indicación acerca del tipo y carácter de los tumores mediastínicos que ocurren clínicamente. Se ha demostrado que la relativa frecuencia en la ocurrencia de los diferentes neoplasmas junto con la edad cuando aparecen clínicamente, el sexo del paciente y la particular ubicación en el mediastino, tienen algún significado. Se notan algunos signos y síntomas y algunas características roentgenológicas que pueden ser sugestivas. Ocasionalmente se puede obtener tejido de una lesión o metástasis externa para hacer un examen biopsico.

Debido a la frecuencia con que existe duda acerca del carácter del neoplasma en casos que al fin y al cabo desarrollan síntomas debidos a malignidad, crecimiento del tumor e infección, parecería que en la mayor parte de los casos se deben explorar y extirpar los tumores o quistes del mediastino cuando lo sea posible, con tal de que no haya signos de metástasis, invasión no extirpable, linfoblastoma o tumor maligno secundario, y si la condición del paciente permite la intervención quirúrgica.

REFERENCES

- 1 Thompson, John V.: "Mediastinal Tumors and Cysts (Collective Review)," *Surg., Gyn. and Obst.* (Internat. Abst. Surg.), 84:195, 1947.
 - 2 Thompson, John V.: "Mediastinal Tumors and Cysts," *J. Ind. State Med. Assoc.*, 40:848, 1947.
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Summary of Talk on Minimal Tuberculous Lesions

Given at the Annual Meeting of the American College of Chest Physicians, Chicago, Illinois, June 20, 1948

The Chairman, Francis J. Weber, M.D., F.C.C.P., introduced the subject by setting forth the following points:

All nations of the world have in the course of history suffered the ravages of tuberculosis. Today, in many nations, this disease still attains epidemic proportions. In the United States, however, certain forces have joined to bring about a gradual reduction in the death rate. What these forces have been, and what their respective roles have been in the reduction of tuberculosis mortality are difficult to assess. We may, perhaps, say that the improvement of social and economic conditions has played a part in the process, as well as improvements in medical practice. Despite our fortuitous situation, however, we cannot be content when tuberculosis still kills about 50,000 Americans every year, and when it may continue to kill countless thousands in years to come.

Epidemiologists, clinicians and public health administrators are vitally concerned with meeting this problem and with preventing most, if not all, of these deaths. All who have studied the problem agree that this can best be accomplished through the early discovery of tuberculosis and the prosecution of similar measures which will make control possible. Early discovery, we are told, can do two things: first, render the individual's prognosis more favorable, and second, through prompt treatment and isolation of infectious cases, prevent spread of the disease to others.

With this introduction, the Panel consisting of an impromptu group of Fellows of the College discussed the subject as follows:

We are experiencing success in finding the minimal cases. The x-ray, which is our principal means of detecting cases of tuberculosis, is finding about seventy per cent of them in a minimal stage. However, the discovery of the minimal case engenders many problems, especially in reference to follow-up.

Unlike the moderately and far-advanced cases found in surveys, almost all of which have symptoms, the minimal case is very frequently symptom-free. When discovered, these cases pose two problems: that of activity and that of the method of follow-up.

Because the minimal case is so often symptomless, even in those cases later proved active, final diagnosis must rely heavily upon bacteriological findings. Where an occasional positive fasting gastric specimen is the only evidence of activity, it should be

confirmed for virulence by injection into guinea pigs. Generally, the "Guide for Disposition of Persons with Abnormal Pulmonary Findings on X-ray Films," published in Public Health Reports, Tuberculosis Control Issue No. 10, is a sound guide to the necessary follow-up.

In treatment, there is no doubt that a large-scale trial on the efficacy of streptomycin in minimal lesions is positively indicated and should prove to be highly valuable. For the purpose of facilitating such critical evaluation, in addition to the improvement of diagnostic work in minimal tuberculosis, laboratory facilities should be promoted, increased in number, and improved in the quality of service. The facilities of the Public Health Service's Atlanta Evaluation Laboratory have been organized to give direct service to localities both in consultation regarding technical problems and in the training of both physicians and laboratory workers in bacteriological science and technique.

In the follow-up of minimal tuberculosis, private and general hospitals can serve a vital function. Their active enlistment in the follow-up program should therefore receive serious consideration.

It is well recognized that the clinical management of minimal tuberculosis will vary with the circumstances of the patient and depend upon the facilities available. At the very least, therefore, rest in bed is indicated for active cases of minimal tuberculosis in order to observe progress more closely.

Finally, it should be acknowledged that the tuberculin test, contrary to the belief tenaciously held until recently, is still an extremely valuable guidepost in the diagnosis of tuberculosis. Its use in the evaluation of minimal lesions must therefore be considered a vital part of the follow-up process along with the serial x-ray and bacteriological examinations.

EDITORIAL

FIFTEENTH ANNUAL MEETING, AMERICAN COLLEGE OF CHEST PHYSICIANS

The Fifteenth Annual Meeting of the American College of Chest Physicians will be held in Atlantic City, June 2 through 5, 1949, under the Presidency of Dr. Richard H. Overholt. Those who have attended the past meetings know of the enthusiasm and interest which characterize these active meetings. Study of the preliminary program published in this issue of the journal of Diseases of the Chest will reveal that the high standards of the past programs have been maintained in both subject matter and participants. Popular features of the previous programs such as the round table luncheons will be repeated, while new features have been added.

In general, the subject matter has been arranged under broad classifications, for example, the surgical session will be held Sunday afternoon while principal discussion of chemotherapy will be Friday morning. The always popular x-ray conference will be held Saturday afternoon under the direction of Dr. M. C. Sosman of Boston. A new feature of the program will be a motion picture session Friday evening, June 3. A group of films will be shown dealing with the many phases of diseases of the chest.

Of special interest will be a ten minute resume of the outstanding work of the year in each of the various sub-specialties of diseases of the chest. The resumes will be given by a leader in each field to briefly cover points of major interest as well as the advances made in his field during the past year.

The program committee has been fortunate in having an unusually wide variety of subjects to choose from in preparing the present program. This is due to the scientific interest and investigative spirit of the members of the College and review of the program will give evidence of this clinical and research activity.

This year's program has been integrated with that of the Section on Diseases of the Chest of the American Medical Association through the cooperation of its chairman, Major General S. U. Marietta, and its Secretary, Dr. Jay Arthur Myers. Members of the College are urged to remain in Atlantic City for the inaugural session of the new Section on Diseases of the Chest and to view the exhibits being prepared for this new Section.

I would like to take this opportunity to thank the members of the program committee, namely, Drs. Edgar Davis, Juan R. Herradora, Edwin R. Levine, Herman J. Moersch, Leo G. Rigler and Harold G. Trimble, for their fine cooperation in preparing the annual program of the College.

Paul H. Holinger, M.D., Chairman,
Committee on Scientific Program.

Fifteenth Annual Meeting of the College

Ambassador Hotel, Atlantic City, New Jersey

June 2 through 5, 1949

Annual Meeting, American Medical Association

Atlantic City, June 6 through 10, 1949

The College will return this year to the Ambassador Hotel in Atlantic City for the Fifteenth Annual Meeting. In 1947 the College held one of its most successful meetings at the same hotel in Atlantic City and it is anticipated that the 1949 session will be equally successful.

If you are planning to attend the meeting it is **EXTREMELY URGENT** that you make your hotel reservations **IMMEDIATELY**. Some of the hotels in Atlantic City have already announced that they are booked to capacity for the dates of the meetings. A convenient form for hotel reservations appears on page vi of this issue of the journal and if you will complete this form and send it to the Executive Offices of the College in Chicago at once, reservations will be made for you in Atlantic City, if possible, at the Ambassador Hotel.

The Committee on Scientific Program of the College, under the chairmanship of Dr. Paul H. Holinger of Chicago, has announced that the program for the 1949 annual meeting is just about completed. The following are some of the papers which will be presented:

"Significance of Positive Cultures,"

I. D. Bobrowitz, M.D., F.C.C.P., Otisville, New York.

"Use of Dihydrostreptomycin in the Treatment of Tuberculosis,"

David T. Carr, M.D., H. C. Hinshaw, M.D., Karl H.

Pfuetze, M.D., F.C.C.P. and H. A. Brown, M.D., Rochester, Minnesota.

"Angiopneumography,"

Lopo de Carvalho, M.D., F.C.C.P., Lisbon, Portugal.

"The Surgical Treatment of Spontaneous Pneumothorax,"

Gerald L. Crenshaw, M.D., F.C.C.P., Oakland, California.

"The Regeneration of Defects of the Trachea and Bronchi:
An Experimental Study,"

Rollin A. Daniel Jr., M.D., Nashville, Tennessee.

"Pulmonary Aspects of Cystic Fibrosis of the Pancreas,"

Lloyd B. Dickey, M.D., F.C.C.P., San Francisco, California.

"Pulmonary Edema,"

Robert M. Eaton, M.D., Grand Rapids, Michigan.

"Thirty Years of Artificial Pneumothorax,"

Peter W. Edwards, M.D., F.C.C.P., Shropshire, England.

"Histoplasmosis,"

Michael L. Furcolow, M.D., Kansas City, Kansas.

"Streptomycin in the Treatment of Miliary and Meningeal Tuberculosis,"

Arnold Shamaskin, M.D., F.C.C.P., Eugene J. Des Autels, M.D., F.C.C.P.
and Henry C. Sweany, M.D., F.C.C.P., Hines, Illinois.

"Surgical Aspects of Pulmonary Calcification,"

Alfred Goldman, M.D., F.C.C.P., Beverly Hills, California.

"The Clinical Evaluation of Disability in Anthracosilicosis,"

Peter A. Theodos, M.D., F.C.C.P., Burgess Gordon, M.D., F.C.C.P.,
Leonard P. Lang, M.D. and Hurley L. Motley, M.D.,
Philadelphia, Pennsylvania.

- "Experiences in Cardiac Valve Surgery,"
Dwight Emory Harken, M.D., Boston, Massachusetts.
- "Bronchial Obstruction,"
Chevalier Jackson, M.D., Philadelphia, Pennsylvania.
- "Surgical Management of Lung Abscess,"
Roy G. Klepser, M.D., Washington, D. C.
- "Cavernostomy,"
Gustav Maurer, M.D., F.C.C.P., Davos, Switzerland.
- "Carcinoma of the Lung; Its Diagnosis by Cytologic Examination of Sputum and Bronchial Secretions,"
John R. McDonald, M.D., Rochester, Minnesota.
- "Pulmonary Fibrosis,"
J. Winthrop Peabody, M.D., F.C.C.P. and J. Winthrop Peabody Jr., M.D., Washington, D. C.; Edward W. Hayes, M.D., F.C.C.P., and Edward W. Hayes Jr., M.D., Monrovia, California.
- "Residual Lesions in Pulmonary Coccidioidomycosis,"
H. E. Bass, M.D., F.C.C.P., A. Schomer, M.D. and R. Berke, M.D., New York, New York.
- "Preliminary Report on the Use of Para Aminosalicilic Acid in Pulmonary Tuberculosis,"
Henry C. Sweany, M.D., F.C.C.P., Chicago, Illinois.
- "The Diagnosis of Congenital Malformations of the Cyanotic Type Amenable to Surgery,"
Helen B. Taussig, M.D., Baltimore, Maryland.

Round Table Luncheon Meetings

A series of round table luncheon meetings will be held on Friday, Saturday and Sunday, June 3, 4 and 5, at the Ambassador Hotel during the annual meeting of the College. Below are listed some of the subjects and moderators for these meetings:

- "Suppurative Diseases of the Lungs," Dr. Evarts A. Graham, St. Louis, Mo.
- "Handling of the Minimal Case," Dr. Peter W. Edwards, Shropshire, England.
- "Pneumoperitoneum," Dr. Andrew L. Banyai, Milwaukee, Wis.
- "Inhalational Therapy," Dr. Alvan L. Barach, New York, N. Y.
- "Status of Pulmonary Resection," Dr. Richard H. Overholt, Brookline, Mass.
- "Atypical Pneumonias," Dr. Italo Volini, Chicago, Ill.
- "B. C. G.," Dr. Robert J. Anderson, Washington, D. C.
- "Bronchial Asthma," Dr. Maurice Segal, Boston, Mass.
- "Dust Diseases," Dr. Oscar Sander, Milwaukee, Wis.
- "Emphysema and Pulmonary Disability," Dr. Edwin R. Levine, Chicago, Ill.
- "Treatment of Tuberculosis in the Aged," Dr. Harold W. Kohl, Tucson, Ariz.
- "When Should Pneumothorax be Terminated," Dr. Harold G. Trimble, Oakland, Calif.
- "Tuberculosis in Children," Dr. W. L. Howard, Northville, Mich.
- "Dosage of New Chemicals and Antibiotics," Dr. Karl H. Pfuetze, Cannon Falls, Minn.

Other subjects to be discussed at the round table luncheon meetings are: "Fungus Diseases," "Chronic Cor Pulmonale in Pulmonary Diseases," "Bronchogenic Carcinoma," and "Boeck's Sarcoid."

The Program Committee appreciates the interest shown by the membership of the College in making suggestions for subjects and moderators for the round table discussions. The suggestions received by the committee were compiled and chosen to meet the popular demand.

Ten - Minute Resumes

One of the new features in the annual program this year will be a ten-minute resume at the close of each scientific session on an important phase of the specialty of diseases of the chest. The following physicians have accepted invitations to present such resumes at the annual meeting: Dr. J. Burns Amberson, "Medical Aspects of Diseases of the Chest"; Dr. Alvan L. Barach, "Respiratory Physiology"; Dr. Brian B. Blades, "Surgery"; Dr. Louis Clerf, "Bronchoesophagology"; and Dr. M. C. Sosman, "Roentgenology."

Luncheon Conferences

Annual Conference of College Chapter Officials:

The Annual Conference of College Chapter Officials will hold a luncheon meeting at the Ambassador Hotel on Thursday noon, June 2. Dr. Charles A. Thomas, Tucson, Arizona, is Chairman of the Conference and Dr. Irving Willner, Newark, New Jersey, is Secretary. Problems of interest to the College Chapters, as well as future activities of the Chapters, will be discussed at the meeting.

Council on International Affairs:

The Council on International Affairs of the College will sponsor a luncheon meeting on Friday, June 3, at which time members from other countries will make presentations.

Council of Tuberculosis Hospitals:

The Council of Tuberculosis Hospitals will hold a luncheon meeting on Saturday, June 4. The activities of the Council, as well as those of the two committees which serve under the Council, namely, the Committee on Sanatorium Standards and the Committee on Rehabilitation, will be discussed at this meeting. Dr. Russell S. Anderson, Erie, Pennsylvania, Chairman of the Council, will preside at this luncheon meeting.

Medical Education:

A luncheon meeting on the subject of medical education will be held on Sunday, June 5, to be presided over by Major General S. U. Marietta, Washington, D. C. The meeting will be addressed by Dr. James E. Paullin, Professor of Clinical Medicine at Emory University Division, Grady Hospital, Atlanta, Georgia, and Brigadier General George E. Armstrong, Deputy Surgeon General, Department of the Army.

X-Ray Conference

An X-ray Conference will be presented on Saturday afternoon, June 4, starting at 2:00 p.m. Members of the College who are interested in presenting x-ray films at the meeting are requested to send their films together with clinical abstract and laboratory findings of the case to Dr. M. C. Sosman, Peter Bent Brigham Hospital, Boston 15, Massachusetts, for consideration. Dr. Sosman will serve as Chairman of the X-ray Conference.

Motion Picture Session

On Friday evening, June 3, a motion picture session will be held at the Ambassador Hotel. Physicians who have interesting motion pictures which they would like to present at this session are invited to make application to Dr. Paul H. Holinger, Chairman, Committee on Scientific Program, American College of Chest Physicians, 500 North Dearborn St., Chicago, Illinois. Applications should include the title of the film, author, approximate running time, whether silent or sound, color or black and white, and the size of the film.

Fellowship Examinations

Oral and written examinations for Fellowship in the College will be conducted at the Ambassador Hotel on Thursday, June 2. Candidates for Fellowship in the College who are eligible to take the examinations should contact the Executive Secretary, American College of Chest Physicians, 500 North Dearborn Street, Chicago, Illinois.

Administrative Session

The Administrative Session of the College will be held on Saturday morning, June 4, at which time the Councils and Committees will report. The election of new officers will follow.

Convocation

The College will conduct a Convocation on Saturday afternoon, June 4, when Fellowship Certificates will be awarded. The Convocation will be conducted by the Board of Regents of the College and a guest speaker will address the assembly.

Cocktail Party and Presidents' Banquet

The Annual Presidents' Banquet will be held on Saturday night, June 4. Dr. Richard H. Overholt, President of the College, will deliver his presidential address and the President-Elect, Dr. J. C. Placak, will be installed as President. The award of the College Medal will also be made at the banquet. A cocktail party will precede the Annual Presidents' Banquet.

Board Meetings

The Board of Regents and Board of Governors of the College will hold their annual meetings on Thursday, June 2, in Atlantic City. The College Councils and Committees will also hold meetings at the time of the annual session in Atlantic City.

Section on Diseases of the Chest

The Section on Diseases of the Chest of the American Medical Association will meet on Wednesday, June 8, and Thursday, June 9, in Atlantic City. There will also be a Section on Diseases of the Chest in the Scientific Exhibits of the American Medical Association at the annual session in Atlantic City.

OFFICIALS OF SOCIETIES PARTICIPATING IN THE VIII CONGRESS OF ULAST, MEXICO CITY, D. F.



Left to right: Ismael Cosío Villegas, M.D., F.C.C.P., President of the VIII Congress of ULAST; Mr. Murray Kornfeld, Executive Secretary of the American College of Chest Physicians; Jorge A. Higgins, M.D., F.C.C.P., President-Elect for the IX Congress of ULAST to take place in Guayaquil, Ecuador, in 1951; Richard H. Overholt, M.D., F.C.C.P., President of the American College of Chest Physicians; and Esmond R. Long, M.D., Executive Secretary of the American Trudeau Society.

VIII Congreso Panamericano de Tuberculosis (ULAST) III Congreso Nacional de Tuberculosis y Silicosis

The VIII Congreso Panamericano de Tuberculosis (ULAST) and the III Congreso Nacional de Tuberculosis y Silicosis were held in Mexico City, Mexico, January 23-29. Physicians numbering 262, representing 20 countries, namely, Argentina, Bolivia, Brazil, Canada, Chile, Costa Rica, Cuba, Dominican Republic, Ecuador, France, Guatemala, Italy, Mexico, Republic of Panama, Peru, Philippine Islands, El Salvador, United States of America, Uruguay and Venezuela, registered for the meeting. The scientific sessions were of a very high caliber and were well attended. The sessions were held at the Cardiological Institute in Mexico City, one of the very few institutes of its kind in the world.

The hospitality of the physicians in Mexico could not be surpassed. Entertainment in the form of dinners, receptions and tours were arranged for the physicians and their wives, and on Saturday evening, January 29, a dinner and grand ball were given at the Hotel del Prado. Dr. Ismael Cosío Villegas, President of the VIII Congress of ULAST, and Dr. Alejandro Celis, the President of the III National Congress of Tuberculosis and Silicosis, as well as the other officers of the Congresses, are to be congratulated for the outstanding meeting which they planned and directed.

The following members of the American College of Chest Physicians attended the VIII Pan American Congress of the Union of Latin America Societies of Tuberculosis (ULAST), and the III National Congress of Tuberculosis and Silicosis, which took place in Mexico City, January 23-29, 1949. Of the 262 registrants, 108 were members of the College:

ARGENTINA (7): Oscar P. Aguilar, Ovidio Francisco R., José Antonio Perez, Gumersindo Sayago, Alberto Jose Soubrie, Raul Vaccarezza, and Jose F. Verna.

BOLIVIA (1): Enrique Vargas Sivila.

BRAZIL (2): Jose Silveira, and Valouis Souto.

CANADA (1): John Carmichael Kovach.

COSTA RICA (2): Arturo Blanco Solis, and Carlos M. Trejos Flores.

CUBA (10): Gustavo Aldereguia Lima, Jose Garcia Arruzaria, Juan J. Castillo, Augusto Fernandez Conde, Luis de la Cruz Muñoz, Rafael Meneses Mañas, Rene G. Mendoza, Antonio Navarrete, Ricardo Sanchez Acosta, and Eugenio Torroella M. Fortun.

DOMINICAN REPUBLIC (1): Juan Moscoso Cordero.

ECUADOR (2): Armando Pareja Coronel, and Jorge A. Higgins.

EL SALVADOR (1): Victor Hugo Lucha.

GUATEMALA (3): Leon Araujo G., Rafael Leal H., and Enrique Coronado Iturbide.

MEXICO (39): Carlos Aguilar, Donato G. Alarcon, Manuel Alonso, Salvador Gomez Alvarez, Rafael Artasanchez, Felipe Aladro Azueta, Ramon Celis Baltazar, Octavio Bandala, Cesar Becerra, Manuel Beltran del Rio, Jesus M. Benitez, Segundo Braña Blanco, Melchor Colon y Camacho, Santiago Caparroso, Mario Martinez Carrouche, Jose F. Colon, Ismael Cosío Villegas, Leopoldo Castro Fernandez, Pedro Alegria Garza, Rodolfo Gil, Elihu J. Gutierrez, Guillermo Solorzano Gutierrez, Rafael Ibarra Perez, Miguel Jimenez, Fernando Katz, Alberto Ladron de Guevara, Vicente A. Moreno, Antenogenes Mundo, Carlos Noble,

COUNCIL ON PAN AMERICAN AFFAIRS, AMERICAN COLLEGE OF CHEST PHYSICIANS, MEXICO CITY, JANUARY 25, 1949



Left to right, 1st row: Fernando Gomez, Uruguay; Gumersindo Sayago, Argentina; Esmond Long, United States; Ismael Cosío Villegas, Mexico; Chevalier L. Jackson, United States; Richard H. Overholt, United States. —*2nd row:* Murray Kornfeld, United States; Attilio Omodei Zorini, Italy; Ovidio Garcia-Rosell, Peru; Herbert L. Mantz, United States; J. Winthrop Peabody, United States; Jose Antonio Perez, Argentina. —*3rd row:* Jose Silveira, Brazil; Horacio Rubio Palacios, Mexico; Manuel Alonso, Mexico; Juan Escudero Villar, Peru; Louis Mark, United States. —*4th row:* Juan M. Moscoso Cordero, Dominican Republic; Raul Soules-Baldo, Venezuela; Juan R. Herrera, United States; Robert J. Anderson, United States; Henry C. Sweany, United States; Raul Vacarezza, Argentina. —*5th row:* Marco Bueno, United States; Carlos M. Trejos Flores, Costa Rica; Arturo Blanco Solis, Costa Rica; Santiago Madeiros, Bolivia. —*6th row:* Enrique Coronado Iturbide, Guatemala; Frank S. Dolley, United States; Arthur Q. Penta, United States; Antonio Navarrete, Cuba; Gustavo Aldereguia, Cuba; Donato G. Alarcon, Mexico; Ricardo Sanchez Acosta, Cuba.

J. Jesus Olivo, Jose Manuel Ortega, Carlos R. Pacheco, Fernando Reborra, Aradio Lozano Rocha, Ubaldo Roldan, Horacio Rubio Palacios, Alberto Sansom, Enrique Staines Davila, Antonio Rios Vargas.

PANAMA (1): Amadeo Vicente Mastellari.

PERU (6): Juan Escudero Villar, Max Espinoza Galarza, Ovidio Garcia-Rosell, Juan Macchiavello, Juan A. Werner, and Humberto Valderrama.

PHILIPPINES (1): Francisco S. Guerrero.

UNITED STATES OF AMERICA (21): Robert J. Anderson, Oscar Auerbach, Marcio Bueno, Frank S. Dolley, Seymour M. Farber, Alfred Goldman, Edward A. Greco, Juan R. Herradora, Chevalier L. Jackson, Edwin R. Levine, Herbert L. Mantz, Louis Mark, Richard H. Overholt, J. Winthrop Peabody, Robert A. Peers, Arthur Q. Penta, G. S. Pesquera, John Robert Phillips, Henry C. Sweany, C. A. Thomas, and Leonid Zavatsky.

URUGUAY (6): Alejandro A. Artagaveytia, Raul Burgos, Cleopatria Epifanio, Fernando D. Gomez, Rene Racine, and Juan Soto Blanco.

VENEZUELA (4): R. Soules-Baldo, Cesar Rodriguez, Julio Rodriguez, and R. Soto Matos.

Meeting, Council on Pan American Affairs

On Tuesday morning, January 25, the Council on Pan American Affairs of the American College of Chest Physicians sponsored a breakfast meeting at the Hotel del Prado to which all officers of the College attending the meeting in Mexico City were invited. Dr. Chevalier L. Jackson, Philadelphia, Chairman of the Council, presided at the meeting and introduced the following officers who presented reports concerning the activities of the College in their countries:

ARGENTINA: Gumersindo Sayago, M.D., Cordoba, Regent and Past-President, Argentine Chapter; Raul F. Vaccarezza, M.D., Buenos Aires, Governor and Past-President, Argentine Chapter; Jose Antonio Perez, M.D., Cordoba.

BOLIVIA: Santiago Medeiros, M.D., La Paz.

BRAZIL: Jose Silveira, M.D., Salvador, Bahia, Governor and President, North Brazilian Chapter.

COSTA RICA: Arturo Blanco Solis, M.D., San Jose; Carlos M. Trejos Flores, M.D., San Jose.

CUBA: Antonio Navarrete, M.D., Havana, Regent; Gustavo Aldereguia, M.D., Havana, Past-President, Cuban Chapter; R. Sanchez Acosta, M.D., Havana, Vice-President, Cuban Chapter.

DOMINICAN REPUBLIC: J. M. Moscoso Cordero, M.D., Trujillo, Governor.

GUATEMALA: Enrique Coronado Iturbide, M.D., Guatemala City, Governor.

MEXICO: Ismael Cosio Villegas, M.D., Mexico City, ULAST President, Governor and President, Mexican Chapter; Donato G. Alarcon, M.D., Mexico City, Regent and Past-President, Mexican Chapter; Miguel Jimenez, M.D., Mexico City, Vice-President, Mexican Chapter; Manuel Alonso, M.D., Mexico City, Past-Secretary, Mexican Chapter; Horacio Rubio Palacios, M.D., Mexico City, Secretary, Mexican Chapter.

PERU: Ovidio Garcia Rosell, M.D., Lima, Regent and Past-President, Peruvian Chapter; Juan Escudero Villar, M.D., Vice-President, Peruvian Chapter; Max Espinoza Galarza, M.D., Lima, Past-President, Peruvian Chapter.

URUGUAY: Fernando Gomez, M.D., Montevideo, Secretary of ULAST and Governor.

VENEZUELA: Raul Soules Baldo, M.D., Caracas.

UNITED STATES OF AMERICA: J. Winthrop Peabody, M.D., Washington, D. C., Past-President and Chairman, Council on Postgraduate Medical Education; Louis Mark, M.D., Columbus, Ohio, First Vice-President; Frank S. Dolley, M.D., Los Angeles, California, Regent; Herbert L. Mantz, M.D., Kansas City, Missouri, Regent; Juan R. Herradora, M.D., Jersey City, N. J., Secretary, Council on Pan American Affairs; Arthur Q. Penta, M.D., Schenectady, N. Y., member, Council on Pan American Affairs; Henry C. Sweany, M.D., Chicago, Illinois, member, Council on Pan American Affairs; Robert J. Anderson, M.D., Washington, D. C., Chairman, Council on Public Health; and Murray Kornfeld, Chicago, Illinois, Executive Secretary of the College.

The meeting was also addressed by Dr. Richard H. Overholt, Brookline, Massachusetts, President of the American College of Chest Physicians. Dr. Esmond R. Long, Philadelphia, Pennsylvania, Executive Secretary of the American Trudeau Society and Editor of the American Review of Tuberculosis and Dr. Attilio Omodei Zorini, Director of the Forlini Institute, Rome, Italy, were invited guests and addressed the conference.

VISITORS TO SANATORIO SAN ANGEL, MEXICO CITY, D. F.



A group of physicians visiting the Sanatorio San Angel, Mexico; during the VIII Congress of ULAST, at the invitation of Dr. Donato G. Alarcon, Medical Director.

MEXICAN CHAPTER SPONSORS LUNCHEON MEETING

The Mexican Chapter of the College sponsored a luncheon meeting at the Paolo Restaurant on Thursday, January 27. All members of the American College of Chest Physicians who were in Mexico City for the Congresses were invited to attend this luncheon. A brief address was given by each of the following:

Donato G. Alarcon, M.D., Mexico City,

Regent of the College for Mexico, Presiding.

Richard H. Overholt, M.D., Brookline, Massachusetts,

President, American College of Chest Physicians.

Chevalier L. Jackson, M.D., Philadelphia, Pennsylvania,

Chairman, Council on Pan American Affairs.

Fernando D. Gomez, M.D., Montevideo, Uruguay, Secretary of ULAST, and Governor of the College for Uruguay.

Mr. Murray Kornfeld, Chicago, Illinois,

Executive Secretary, American College of Chest Physicians.

Dr. Manuel Alonso, past secretary of the Mexican Chapter, was introduced and complimented for his efforts in arranging the luncheon meeting. Dr. Horacio Rubio Palacios, the new secretary of the chapter, was also introduced.

Visitors to the United States of America

Following the meeting of the VIII Pan American Union of Latin American Tuberculosis Societies (ULAST) and the III National Congress of Tuberculosis and Silicosis in Mexico City, a number of College members from various parts of the world visited clinics, hospitals and the Executive Offices of the College during a tour of the United States of America. Some of the members were accompanied by their wives.

ARGENTINA:

From the Argentine came Dr. Raul F. Vaccarezza, Governor of the College for Argentina, Dr. Alberto Jose Soubrie, Mrs. Vaccarezza and Mrs. Soubrie. They flew from Mexico City to Havana, Cuba, and then traveled to New York City via Miami. They were met in New York City by Dr. Juan R. Herradora, Secretary of the Council on Pan American Affairs for the College, and were entertained by Dr. Herradora during their stay in New York City. Drs. Vaccarezza, Soubrie and their wives returned to Buenos Aires via New Orleans.

BRAZIL:

From Brazil came Dr. Jose Silveira, Governor of the College for North Brazil and President of the North Brazilian Chapter of the College. Dr. Silveira visited Los Angeles, San Francisco, Denver, Chicago, Washington, D. C., Philadelphia and New York City. While in Philadelphia, Dr. Silveira attended the postgraduate course in diseases of the chest sponsored by the Pennsylvania Chapter of the College and the Laennec Society of Philadelphia, held at the Warwick Hotel from February 28 through March 4. Dr. Silveira visited the tuberculosis hospitals and clinics in California and in Denver where he delivered a lecture at the

GUESTS OF DR. AND MRS. JUAN R. HERRADORA, SECRETARY OF THE COUNCIL ON PAN AMERICAN AFFAIRS



Left to right, standing: Dr. Juan Soto Blanco; Dr. Juan R. Herradora, Secretary of the Council on Pan American Affairs; Dr. Raul Burgos; Dr. Raul Vaccarezza; Dr. Fernando D. Gomez; Dr. Jose Silveira; Dr. Alejandro A. Artagaveytia. —*Seated:* Mrs. Artagaveytia; Mrs. Soto Blanco; Mrs. Herradora; Mrs. Vaccarezza. —*On floor:* Dr. Cleopatria Epifanio; Dr. Alberto J. Soubrie and Mrs. Soubrie.

National Jewish Hospital on 'B.C.G. Vaccine in Brazil.' In Chicago, Dr. Silveira was the guest of honor at a dinner sponsored by the Illinois Chapter of the College at the Congress Hotel on February 11, and he spoke on "The World Organization of the College." While in Chicago, Dr. Silveira addressed a staff meeting at the Municipal Tuberculosis Sanitarium on "Pulmonary Schistosomiasis in Brazil." He spent some time at the Executive Offices of the College in Chicago discussing the organization of the College in Brazil. In Brazil at the present time there are four College Chapters and the organization of a fifth chapter is contemplated. While in the East, Dr. Silveira visited the Fall River Tuberculosis Hospital, Fall River, Massachusetts, as a guest of Dr. Marcio Bueno, where he gave a paper before the hospital staff on "The Advantages of Oral B.C.G. Vaccination."

DOMINICAN REPUBLIC:

From the Dominican Republic came Dr. Juan Moscoso Cordero, Governor of the College for the Dominican Republic. Following a brief visit in Los Angeles, Dr. Moscoso Cordero visited the Executive Offices of the College in Chicago. He then went on to New York City where he spent several weeks visiting hospitals and clinics in the metropolitan district.

GUATEMALA:

From Guatemala came Dr. Rafael Leal, President of the Central American Chapter of the College, and Dr. Jose Colon. These physicians also visited Los Angeles and San Francisco, California.

ITALY:

From Italy came Dr. Attilio Omodei Zorini, Director of the Forlanini Institute of Rome. He flew from Mexico City to New York City, where he visited Seaview Hospital as the guest of Dr. David Ulmar. Dr. Zorini then flew to Chicago for a visit with Mr. Murray Kornfeld, Executive Secretary of the American College of Chest Physicians. He was guest of honor at a dinner given at the Palmer House, Chicago, on February 5. Among others, the dinner was attended by Dr. and Mrs. Juan Escudero Villar, and Dr. and Mrs. Humberto Valderama, Lima, Peru; Dr. Juan Moscoso, Trujillo, Dominican Republic; Mrs. E. W. Hayes, Monrovia, California; Dr. and Mrs. Italo Volini, Dr. and Mrs. Minas Joannides, Dr. and Mrs. Edwin R. Levine and Dr. and Mrs. Henry C. Sweany, all of Chicago; and Dr. James R. Perkins, Managing Director of the National Tuberculosis Association, New York City. Mr. and Mrs. Murray Kornfeld and Miss Harriet Lumm of the Executive Offices of the College also attended the dinner.

PERU:

From Peru came Dr. Ovidio Garcia Rosell, Regent of the College; Dr. Max Espinoza Galarza, past president of the Peruvian Chapter of the College, and Dr. Juan Macchiavello. They visited Los Angeles and San Francisco, California. Dr. Juan Escudero Villar, Vice-President of the Peruvian Chapter and Dr. Humberto Valderrama flew direct from Mexico City to Chicago, where they visited a number of hospitals, clinics and the Executive Offices of the College. They were guests at a dinner given in their honor at the Palmer House on February 5. They were accompanied by Mrs. Escudero Villar and Mrs. Valderrama. From Chicago

they went to New York City and Washington, D. C. In New York City they were greeted by Dr. Juan R. Herradora, Jersey City, New Jersey.

PHILIPPINE ISLANDS:

From the Philippine Islands came Dr. Francisco S. Guerrero, Chief Surgeon of the Quezon Institute, Manila. Dr. Guerrero visited a number of hospitals, clinics and the Executive Offices of the College in Chicago as a part of his itinerary, which included visits to a number of medical centers throughout the world. Dr. Guerrero plans on spending several months in the United States, and will then leave for Europe before returning to the Philippine Islands.

URUGUAY:

From Uruguay came Dr. Fernando D. Gomez, Governor of the College for Uruguay, Dr. Alejandro Artagaveytia, Dr. Raul Burgos, Dr. Cleopatra Epifanio, Dr. Rene Racine and Dr. Juan Soto Blanco. Mrs. Artagaveytia and Mrs. Soto Blanco accompanied their husbands to the United States of America. They flew from Mexico City to Los Angeles, where they were the guests of Dr. Frank S. Dolley, Regent of the College for California, Dr. Lyman A. Brewer, III, Vice-President of the California Chapter of the College and Dr. Alfred Goldman. While in Los Angeles they visited Olive View Sanatorium, Duarte Sanatorium and the Veterans Hospital at San Fernando. They next visited San Francisco where they were the guests of Dr. Seymour M. Farber, Secretary of the California

URUGUAYAN DELEGATION ARRIVES IN CHICAGO, ILLINOIS



Left to right, top row: Dr. Rene Racine, Dr. Alejandro C. Artagaveytia, Dr. Juan Soto Blanco. —Bottom row: Dr. Raul Burgos, Dr. Fernando D. Gomez, Dr. Cleopatria Epifanio and an airline hostess for the United Airlines.

Chapter of the College and Dr. M. A. Benioff. They then visited Denver, Colorado, where they were greeted by Dr. W. Bernard Yegge, Secretary of the Rocky Mountain Chapter of the College.

The next stop on their itinerary was Chicago, and following a visit to the Executive Offices of the College their stay in Chicago was taken up by visits to the hospitals and clinics. They were the guests at the Municipal Tuberculosis Sanitarium of Dr. Henry C. Sweany, member of the Council on Pan American Affairs of the College and Dr. Sol Roy Rosenthal, Director of the Tice B.C.G. Clinic at the Cook County Hospital. A dinner was given in their honor at the Hotel Moraine, Highland Park, Illinois, on Sunday, February 13. This dinner was also attended by Dr. Jose Silveira of Brazil.

After leaving Chicago, they flew to Washington, D. C., and then on to New York City, where they were greeted and entertained by Dr. Juan R. Herradora, Secretary of the Council on Pan American Affairs in the College. The doctors and their wives were guests of Dr. Chevalier L. Jackson, Chairman of the Council on Pan American Affairs of the College in Philadelphia on February 28. Enroute from New York City to Uruguay they stopped off at San Juan, Puerto Rico, where they were guests of the Puerto Rican Chapter of the College. Some of the doctors stopped off for brief visits at Trinidad and Rio de Janeiro, while the others proceeded direct to Montevideo, Uruguay.

College Chapter News

NEW JERSEY CHAPTER

The annual meeting of the New Jersey Chapter will be held at the Ambassador Hotel, Atlantic City, in conjunction with the annual meeting of the Medical Society of New Jersey, April 25-28. The chapter will hold a luncheon meeting on April 28. The following scientific program will be presented in the Section on Chest Diseases of the Medical Society of New Jersey:

"Experience with Para Amino Salicylic Acid in the Treatment of Tuberculosis,"

Benjamin P. Potter, M.D., F.C.C.P., Jersey City.

Discussant: Emanuel Klosk, M.D., F.C.C.P., Newark.

"Treatment of the Unexpandable Lung,"

Paul Geary, M.D., Scotch Plains.

Discussant: Philip J. Kunderman, M.D., New Brunswick.

"Cor Pulmonale, Its Relationship to Pulmonary Disease, Cause and Effect,"

Paul K. Bornstein, M.D., F.C.C.P., Asbury Park.

Discussant: Irving L. Applebaum, M.D., F.C.C.P., Newark

"The Second Most Important Silent Lesion,"

Richard H. Overholt, M.D., F.C.C.P., Brookline, Massachusetts.

Discussant: George N. J. Sommer Jr., M.D., Trenton.

Dr. Joseph A. Smith is Chairman of the Section on Chest Diseases and Dr. Juan R. Herradora is Secretary. Dr. Edwin R. Levine of Chicago, will present a paper on B.C.G. in the Section on Pediatrics of the Medical Society of New Jersey.

OHIO CHAPTER

The Ohio Chapter of the College will hold its annual meeting in Columbus on April 20, in conjunction with the Ohio State Medical Association meeting, April 19-21. The chapter will hold a luncheon meeting at the Neil House which will be followed by the business meeting. A scientific program as follows will be presented after the business meeting:

"Pneumoperitoneum,"

William J. Habeeb, M.D., F.C.C.P. and
Howard Reiser, M.D., F.C.C.P., Springfield, Ohio.

"Experience with Papanicolaou Technique in the Diagnosis of
Pulmonary Malignancies,"

Neil Andrews, M.D., F.C.C.P., Walter Baum, M.D., F.C.C.P. and
Karl P. Klassen, M.D., F.C.C.P., Columbus, Ohio.

X-Ray Conference.

PACIFIC NORTHWEST DISTRICT CHAPTER

The annual meeting of the Pacific Northwest District Chapter of the College was held in Portland, Oregon, Friday and Saturday, November 5 and 6, 1948. Scientific sessions were held in the University of Oregon Medical School Library Auditorium. Dr. Paul Samson of Oakland, California, was guest speaker.

New chapter officers elected at the business meeting were:

W. Elliott Harrison, M.D., Vancouver, B. C., President.
Frederick Slyfield, M.D., Seattle, Washington, Vice-President.
Florence A. Brown, M.D., Portland, Oregon, Secretary-Treasurer.

Mrs. William S. Conklin entertained the physicians' wives at tea in her home Friday afternoon.

In the evening an informal banquet at the University Club was attended by wives and guests as well as member physicians, with about seventy persons present. The retiring President, Dr. Grover Bellinger, accorded recognition to the memory of three members lost by death during the past year, namely, Dr. Philipp Schonwald, Seattle, Dr. Leon G. Woodford, Everett, Washington, and Dr. Irvin R. Fox, Eugene, Oregon.

Speaker of the evening was Dr. Howard P. Lewis, Professor and Head of the Department of Medicine, University of Oregon Medical School. He talked on "Some Aspects of Education in Chest Diseases." He stressed, first, the advances made in the treatment of chest diseases in the last two decades, and second, the need for full utilization of physical examination and careful interpretation of positive findings before requesting costly laboratory procedures.

WISCONSIN CHAPTER

The Wisconsin Chapter of the College held meetings in Milwaukee on January 28 and on February 25. Dr. Ross Weller presented a talk on "Bacterial Allergy" at the January meeting, and Dr. Mischa Lustok discussed "Myocarditis" at the meeting held in February.

ILLINOIS CHAPTER

The annual meeting of the Illinois Chapter of the College will be held at the Palmer House, Chicago, on Sunday, May 15, preceding the annual meeting of the Illinois State Medical Society, May 16-18, 1949. The following scientific program will be presented by the chapter commencing at 2:00 p. m.:

- "Pulmonary Manifestations of Sarcoidosis,"
Andrew L. Banyai, M.D., F.C.C.P., Milwaukee, Wisconsin.
- "Cavernostomy in Pulmonary Tuberculosis,"
John V. Thompson, M.D., F.C.C.P., Indianapolis, Indiana.
- "The Treatment of Chronic Pulmonary Suppurations,"
William M. Tuttle, M.D., Detroit, Michigan.
- "Decortication of the Lung in the Treatment of Empyema,"
Thomas H. Burford, M.D., St. Louis, Missouri.
- Subject to be announced,
Leo G. Rigler, M.D., F.C.C.P., Minneapolis, Minnesota.

A business meeting will be held following the scientific program. A guest speaker to be announced will address the dinner meeting of the chapter, Sunday night, May 15.

ARIZONA CHAPTER

The Arizona Chapter will hold its annual meeting in Tucson in conjunction with the annual meeting of the Arizona State Medical Association, May 8-10, 1949. A scientific program on diseases of the chest will be presented at the chapter meeting.

PUERTO RICO CHAPTER

The Puerto Rico Chapter of the College held its annual meeting on December 11 in conjunction with the annual meeting of the Puerto Rico Medical Association. A business meeting was held in the morning which was followed by a luncheon at the Navy Beach Club, San Juan. After the luncheon the following scientific program was presented:

- "Combination Pneumothorax-Pneumoperitoneum in the Therapy of Pulmonary Tuberculosis,"
Jose L. Porrata, M.D., Santurce.
- "Mixed Bronchial Tumor" (Presentation of a Case),
David Rodriguez Perez, M.D., Rio Piedras.
- "Tumors of the Lung and Mediastinum" (Presentation of Cases),
Luis A. Passalacqua, M.D., F.C.C.P., Santurce.
- "Radical Surgery in Extrinsic Cancer of the Larynx"
(Preliminary Report),
David Rodriguez Perez, M.D., Rio Piedras, and
Jose Pico, M.D., F.C.C.P., Santurce.

The following officers of the chapter were elected for the year 1949:

- Dr. Angel M. Marchand, President.
- Dr. Pedro J. Durand, Vice-President.
- Dr. Ezequiel Martinez Rivera, Secretary-Treasurer.
- Dr. Hector Marrero Otero, Dr. Juan H. Font, and
Dr. Leandro Santos, Board Members.

CALIFORNIA CHAPTER

The annual meeting of the California Chapter of the College will be held in Los Angeles in conjunction with the annual meeting of the California Medical Association, May 8-11, 1949. An interesting program on chest diseases is being prepared for presentation at the meeting.

NEW YORK STATE CHAPTER

The New York State Chapter will hold its annual meeting in Buffalo in conjunction with the annual meeting of the Medical Society of the State of New York, May 2-6, 1949. An interesting program will be presented in the Section on Diseases of the Chest in the state medical society.

CENTRAL AMERICAN CHAPTER

The Central American Chapter held its II Annual Reunion at the Sanatorio Antituberculoso, Guatemala, on January 19, 1949, in conjunction with the III Central American Congress of Tuberculosis. An excellent scientific program was presented. Amadeo Vicente Mastellari, M.D., F.C.C.P., Republic of Panama, Regent of the College for Central America, was the guest of honor.



Second Annual Meeting of the Central American Chapter of the American College of Chest Physicians, Guatemala, January 19, 1949.

VIRGINIA CHAPTER

The annual meeting of the Virginia Chapter was held at the Richmond Veterans Administration Hospital on March 1, with Dr. Dean B. Cole, President, presiding. There were 75 physicians in attendance including a large delegation from the Potomac Chapter and other guests from West Virginia and North Carolina. The new officers elected for the chapter are as follows: Dr. E. C. Drash, President; Dr. Kinloch

Nelson, Vice-President; and Dr. C. W. Scott, Secretary-Treasurer. The following scientific program was presented:

"Recent Advances in Resection and Cavernostomy,"
J. D. Murphy, M.D., F.C.C.P., Oteen, North Carolina.

"Pneumoperitoneum,"
R. E. Moyer, M.D., F.C.C.P., Oteen, North Carolina.

"Laboratory Aids in Fungus Diseases,"
Abraham Rosensweig, Ph.D., Richmond, Virginia.

"Bronchogenic Carcinoma,"
Paul Kriz, M.D., Richmond, Virginia.

"Blastomycosis,"
J. P. Williams, M.D., Richmond, Virginia.

The next meeting of the Virginia Chapter will be held at the Chamberlayne Hotel, Old Point Comfort, Virginia, during the meeting of the state medical society, May 2 to 5, 1949.

College News Notes

Dr. Francis L. Lederer, Professor and Head of the Department of Otolaryngology, University of Illinois College of Medicine, recently conducted a survey of hearing and speech needs in Mexico, at the invitation of the Under-Secretary of Health and Welfare of Mexico. Dr. Lederer also participated in the first postgraduate course in otolaryngology offered by the University of Mexico Medical School.

Dr. Ralph H. Homan, El Paso, Texas, has been elected President-Elect of the El Paso County Medical Society.

Dr. John S. Harter, Louisville, Kentucky, has accepted an invitation to participate in the 1949 session of the Texas State Medical Association which is to be held in San Antonio, May 3-5.

Dr. Eli H. Rubin, New York City, has been named director of medicine and chairman of the medical staff at Seton Hospital in the Bronx, a 500 bed tuberculosis institution taken over by the city last May.

Dr. George W. Waldron, Houston, Texas, has been elected President-Elect of the Harris County Medical Society.

Obituaries

GEORGE CHAMBERS ANGLIN
1890 - 1948

Following a full day's Medical duties on Tuesday, April 16th, 1948, Dr. Anglin suffered an almost immediately fatal heart seizure during that night.

Born in Ireland, Dr. Anglin came to Canada in 1907, and graduated from the University of Toronto in 1914. He served in the R.A.M.C. from

1915 to 1918. He continued as Director of the Chest Clinic at Christie Street Military Hospital and during the Second World War, was Chest Consultant for the three services in the Toronto Military District. For his services in the same capacity to the Norwegian Air Force he was signally honored by the King of Norway.

He was a member of the Staff of the Toronto Western Hospital and enjoyed a large consulting practice in allergic and chest diseases. His interests were international. In addition to his Canadian affiliations he was a member of many other medical bodies including the American College of Physicians, the Trudeau Society, American Academy of Allergists and the American Board of Internal Medicine. He was one of the early Canadian Fellows of the American College of Chest Physicians and active in promoting its interests. He was a member of the Senate of the University of Toronto from 1944, President of the Medical Alumni Association of the University in 1945-46 and included amongst his activities those of the Church and Philanthropic bodies.

The profession in Canada has suffered a severe loss in his untimely death.

H. I. Kinsey, Governor for Ontario.

IRVIN REGINALD FOX

1891 - 1948

With the passing of Dr. Irvin Reginald Fox of Eugene, Oregon, on September 21, 1948, the community and the medical profession suffered a severe loss. He was an indefatigable, conscientious worker, a keen thinker and able diagnostician. None, either the rich or poor, the distinguished or unknown, were denied his services, and his humanitarian attitude won him many friends among the laity. Knowing that the end was near unless he rested from his exacting duties, his only thought was the comfort and the welfare of his patients which led directly to his untimely death. All who had the privilege of knowing Dr. Fox will miss his friendly smile and counsel.

His practice was limited to Internal Medicine but his main interest was in diseases of the chest, especially cardiology and tuberculosis.

He was a Fellow of the American College of Chest Physicians, a Fellow of the American College of Physicians and a member of the American Heart Association, a member of his County Medical Society, of the Oregon State Medical Society and a member of the American Medical Association. He was formerly Chief of Staff of the Sacred Heart Hospital in Eugene, Oregon and a member of the Medical Examining Board of the State of Oregon and its former president. At the time of his death, he was Chief of the Medical Section of the Staff of the Sacred Heart Hospital in Eugene, Oregon.

He was born in Oregon City, Oregon, on January 25, 1891. He was graduated from the University of Oregon in 1917 and the University of Oregon Medical College in 1921. Shortly after that, he located in Eugene after taking a residency in medicine. He married Edyl Fraasch in 1917 who survives him along with two children.

J. M. Odell, M.D., Governor for Oregon.